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# Biennial Report of the Director, National Institutes of Health



Volume 1  
1985-1986



U.S. DEPARTMENT  
OF HEALTH AND  
HUMAN SERVICES  
Public Health Service  
National Institutes  
of Health



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# The Biennial Report of the Director, National Institutes of Health

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## Foreword

I am pleased to transmit to Congress and the American people the first Biennial Report of the Director, National Institutes of Health (NIH). The NIH began in 1887 as the Hygienic Laboratory, a one-room facility in the Marine Health Service Hospital on Staten Island, and after several changes in name as well as location, has grown to become the leading institution in the world dedicated to improving human health through the conduct of biomedical research. Fiscal year 1987 will be observed as NIH's centennial year, celebrating "A Century of Science for Health." The centennial provides an occasion for creating a better understanding among the American people of the importance of biomedical research—an opportunity to convey a sense of its accomplishments and promise for the future.

The role of biomedical research in improving human health is not always readily understood. Biomedical research is deeply rooted in biology and calls upon many disciplines to increase knowledge about the processes underlying health, disability, and disease, to synthesize this knowledge into useful form, and to extend it to specific interventions that improve health. In this unprecedented era of discoveries in molecular biology, genetics, immunology, and neurobiology, scientists are coming closer than ever before in the history of medicine to understanding the basic mechanisms of

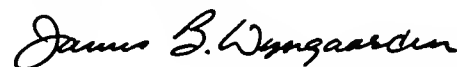
living processes in cells and tissues, and there is a high degree of confidence that the underlying mechanisms of disease are becoming approachable because of these insights.

Significant progress is occurring across all frontiers of science. For example, tremendous advances against acquired immune deficiency syndrome (AIDS) are being made. New insights about the basic structure of the virus, how its replication is controlled, and how it destroys certain target cells may prove crucial to the eventual discovery of effective agents for the prevention and treatment of AIDS. At the same time, a new approach to cancer treatment using interleukin-2 to activate the immune system to destroy cancer cells has been developed. Gains against genetic diseases are being made. A genetic marker for cystic fibrosis has been found, bringing scientists closer to identifying the gene itself and to discovering the basic defect causing this fatal inherited disease. Great strides are also being made in dealing with the complications of diabetes. One treatment approach, the transplantation of donor pancreas islet cells is progressing rapidly and offers great hope of providing recipients with a close facsimile of the normal functioning of the pancreas.

To a large extent the advances in biomedical research today determine medical practice available

tomorrow. From the results of research come the means of improving the quality of health care and, ultimately, of reducing its costs. Although certain technological advances may initially appear to increase health care costs, improved modes of diagnosis, treatment, and prevention eventually yield an overwhelming return on the research investment. Recent advances such as drug treatment rather than surgery for patent ductus arteriosus (a serious heart defect of infants), drug treatment of coronary artery disease instead of coronary bypass surgery in certain patients, and newly developed laser treatment for serious eye disease will reduce significantly costs associated with dealing with these health problems.

This time also provides an occasion to reinforce a set of relationships forged between the Executive and Legislative Branches of Government with the academic community and private industry that has moved this Nation to a position of world leadership in health research. Each of these partners has influenced significantly the shaping of this country's biomedical research enterprise, and each can take great pride in reviewing the achievements and advances that have been set forth in this report.



James B. Wyngaarden, M.D.  
Director  
National Institutes of Health



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## Executive Summary

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### Background

The Biennial Report of the Director, National Institutes of Health (NIH), is the first report on the Nation's biomedical research effort submitted by the Secretary of the Department of Health and Human Services to the President and Congress of the United States, pursuant to Section 403 of the Health Research Extension Act of 1985. The date for the submission of this report was extended to December 1, 1985. This report was prepared at an estimated cost of \$119,000, which was shared by all NIH research Institutes and Divisions, as well as the NIH Director's office, and represents an overestimate since this document will serve multiple purposes.

As specified by the Act, the report is organized around five major topics:

- Advances, Opportunities, and Issues in Biomedical Research
- Improvements in Grant and Contract Accountability and Technical and Scientific Peer Review
- NIH Research in Disease Prevention
- Biennial Reports of the NIH Institutes and Research Divisions
- Biennial Reports of the National Advisory Councils and Boards

The report is presented in two volumes. Volume I presents the first four topics prescribed by the Act; Volume II contains the Biennial Reports of the National Advisory Councils and Boards. Also, Section 433 of the Act requires an evaluation of the arthritis, diabetes, and digestive disease centers. These evaluations are provided in Volume I, Section 4, at the end of the Biennial Reports of the Director of the National Institute of Diabetes and

Digestive and Kidney Diseases and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

### Highlights

Biomedical research is moving forward at an unprecedented pace. Key discoveries in molecular biology, genetics, and immunology have led to the widespread use of techniques that are enabling scientists to address fundamental questions about the nature of living organisms. It is now possible to alter protein activity, to isolate components in developmental processes, and to repair defective enzyme functions using recombinant DNA and protein engineering techniques. Cells and bacteria can be transformed into factories to produce custom-made monoclonal antibodies or valuable hormones and growth factors. These advances, which have been made in the past decade, are still diffusing into existing fields of investigation. Questions that went unanswered for lack of appropriate technology are now under attack. Their solutions will accelerate our progress against disease, as well as raise new questions to explore.

This report offers many examples of recent advances and opportunities for future progress in biomedical research. Programs sponsored by NIH encompass the entire spectrum of human disease and have led to numerous achievements in diagnosis, treatment, prevention, and understanding of the physiologic processes underlying disease states. The selections described are not intended to provide a comprehensive listing of contributions NIH has made toward improving the health of the Nation, but rather to illustrate the scope of the research effort.

The NIH makes approximately 25,000 extramural awards to more than 1,200 institutions in every state of the Union and to a number of foreign countries. Awards are provided through research project grants, cooperative agreements, research contracts, research center grants, research career development support, national research service support, and a variety of other research and research training grants. These awards are reviewed through the two-tiered peer review process, are subject to administrative policies and procedures, and are managed through a variety of extramural processes. Each year the NIH undertakes initiatives designed to improve policy and procedures governing the administration of extramural activities and the peer review process. Highlighted in the report are some of the initiatives undertaken in FY 1985.

The report also describes NIH prevention research activities. Research into the prevention of disease has increased in complexity due to a shift in the relative prevalence of chronic diseases such as cancer and diabetes as compared to infectious diseases such as pneumonia and tuberculosis—the latter were more common at the beginning of the century. In the past, prevention research has focused on serious infectious diseases caused by bacteria and viruses. Now it must cover a multitude of other types of diseases with many diverse causes, methods of occurrence, and disease mechanisms, many of which are as yet unknown. At the NIH the prevention of disease, disability, and other health problems is a priority for research, especially in this era of demographic change where chronic disease is increasingly important

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and the consequent need to reduce rising health care costs is imperative.

The NIH has long been involved in prevention-related research, although such activities have not always been so identified. The main goal of the NIH is to acquire new biomedical knowledge that ultimately can be used to prevent disease, since prevention clearly is the most useful extension of knowledge in the health field. At the NIH, research in prevention has the dual objectives of protecting individuals from disease and preventing the progression of disease to disability or death. Prevention research occurs along a spectrum from the quest for new scientific knowledge to the dissemination of proven findings.

## Conclusion

Fiscal year 1987 will be observed as NIH's centennial year, celebrating "A Century of Science for Health." The centennial provides an occasion for creating a better understanding among the American people of the importance of biomedical research—an opportunity to convey a sense of its accomplishments and promise for the future. This time also provides an occasion to reinforce a set of relationships forged between the Executive and Legislative Branches of Government with the academic community and private industry that has moved this Nation to a position of world leadership in health research. Each of these partners has influenced significantly the shaping of this country's biomedical research enterprise, and each can take great pride in reviewing the achievements and advances that have been set forth in this report.

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# **Section 1**

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**Advances,  
Opportunities,  
and Issues  
in Biomedical  
Research**

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# Advances, Opportunities, and Issues in Biomedical Research

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## Introduction

This Biennial Report of the Director, National Institutes of Health (NIH), describes recent advances and opportunities for future progress in biomedical research. Major science policy issues are also discussed. These presentations represent highlights only and are intended to illustrate the scope and promise of the Nation's biomedical research effort. In addition, the report also provides an overview of the NIH structure.

## Overview of the NIH Structure

### Mission

The mission of the National Institutes of Health is to improve the health of the Nation by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; and developing and improving methods of preventing, detecting, diagnosing, and treating disease.

NIH accomplishes this mission through the:

- Support of biomedical research in universities, hospitals, and research institutions in this country and abroad.
- Conduct of biomedical research in its own laboratories and clinics.
- Support of training for promising young researchers.
- Development and maintenance of research resources.
- Identification of research advances that have significant potential for clinical application, and the facilitation of the transfer of such advances to the health care system.

- Promotion of effective ways to communicate biomedical information to scientists, health practitioners, and the public.

### Legislative Base

The basic legislative authorities underlying all NIH activities are contained in the Public Health Service (PHS) Act. That act, primarily through provisions in Titles III and IV, authorizes all NIH-sponsored research, including both intramural and extramural programs; research training; information dissemination; health promotion and disease prevention activities; clinical studies and associated patient treatment; and NIH participation in cooperative research-related endeavors with other countries and in the training of foreign scientists. The Health Research Extension Act of 1985, P.L. 99-158, enacted in November 1985, amended the Public Health Service Act and authorized in law NIH as an agency of the PHS, defined the duties and responsibilities of the NIH Director, and included authorization for every research Institute, the Division of Research Resources, the Fogarty International Center, a new National Center for Nursing Research, and the National Library of Medicine as agencies of NIH. Underlying all of these authorities is the general research authority of the Secretary under Section 301 of the PHS Act.

Public Law 99-158 included the establishment of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In effect, this legislation divided the former National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) into two Institutes—the NIAMS and the

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Implementation of this change will take part in three phases over fiscal years 1986 through 1988. Currently, efforts are proceeding to appoint a permanent Director and to establish an independent Advisory Council for each of the new Institutes. Another provision of the law established a National Center for Nursing Research (NCNR). A number of steps have been taken toward implementation of this mandate, such as reviewing the staff, budget, and space requirements; developing a charter for the NCNR Advisory Council and a nursing research study section in the NIH Division of Research Grants; identifying office space to house Center activities; and appointing an acting director and a search committee to assist in selecting a permanent director.

### Organizational Structure

To carry out its mission and legislative mandates, the NIH is organized into an Office of the Director (OD), twelve research Institutes, one research Division, one research Center, three service Divisions, and the National Library of Medicine. The organization also includes the Clinical Center—a combined research hospital and laboratory complex—and Fogarty International Center, which fosters international biomedical research collaboration. All of the NIH Institutes, the Division of Research Resources, the National Center for Nursing Research, the Fogarty Center, and the National Library of Medicine have individual congressional appropriations. In total, the NIH receives 18 separate appropriations each year.

The typical NIH Institute includes both an extramural and an intramural program component. The

extramural programs are responsible for roughly 80 percent of NIH resources in the form of research grants or contracts. Through these programs, NIH makes approximately 20,000 awards of various kinds to more than 1,200 institutions in every state of the Union and to a number of foreign countries. Extramural awards are based on a two-tiered peer review assessment—one for technical merit and one for program relevance. Nearly all of the NIH Institutes also have an intramural component of laboratory and clinical research programs. Over 2,500 research projects are in progress at all times, making NIH the largest center for biomedical and behavioral research in the world. The intramural program, while smaller in terms of dollars (roughly 13 percent of the annual NIH budget), requires somewhat more than half of total personnel resources for direct laboratory and clinical research on the Institutes' assigned problems. Boards of Scientific Counselors are responsible for assessing the quality and direction of the intramural program. The Office of the Director provides scientific and policy leadership and oversight and plays a coordinating role in a number of cross-cutting science activities, such as acquired immune deficiency syndrome (AIDS) and biotechnology, and oversees the implementation of a variety of program initiatives, such as nutrition and disease prevention.

## **A Century of Science for Health**

### **Centennial Celebration**

In 1987, the NIH will celebrate 100 years of biomedical research, or, as the centennial theme states, "A Century of Science for Health." The NIH began as the Hygienic Laboratory, a one-room facility in the Marine Health Service Hospital on Staten Island. The sole researcher was Dr. Joseph Kinyoun, a physician and bacteriologist who worked in the labs of Pasteur and Koch. The Hygienic Laboratory moved to Washington in 1891, and the Ransdell Act of 1930 designated the Hygienic Laboratory as the National

Institute of Health. The cornerstone for the first building at the Bethesda campus was laid June 30, 1938. Since then, the NIH has grown to over 40 buildings encompassing 311 acres.

In celebrating this century of achievement, the NIH views the centennial as more than an institutional birthday. It provides an occasion for creating a better understanding among the American people of the importance of biomedical research—an opportunity to convey a sense of its accomplishments and promise. The centennial also provides an opportunity to reinforce a set of relationships forged between the Executive and Legislative Branches of Government with the academic community and private industry that has moved this Nation to a position of world leadership in health research.

### **The Role of Biomedical Research**

The role of biomedical research in improving human health is not always readily understood. Biomedical research is deeply rooted in biology and calls upon many disciplines to increase knowledge about the processes underlying health, disability, and disease; to synthesize this knowledge into useful form; and to extend it to specific interventions that improve health. In this unprecedented era of discoveries in molecular biology, genetics, immunology, and neurobiology, scientists are coming closer than ever before in the history of medicine to understanding the basic mechanisms of living processes in cells and tissues, and there is a high degree of confidence that the underlying mechanisms of disease are becoming approachable because of these insights.

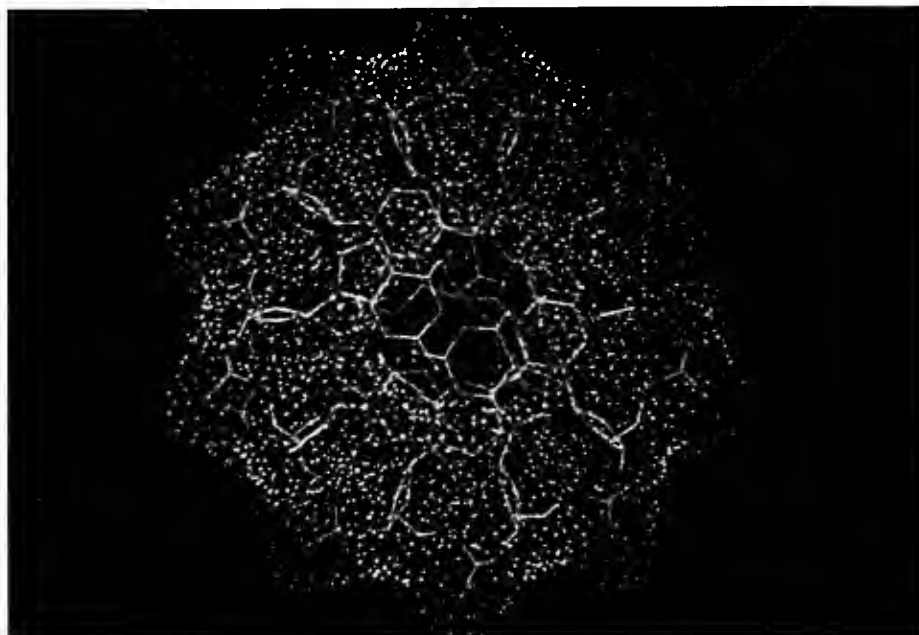
Significant progress is occurring across all frontiers of science. For example, tremendous advances against AIDS are being made. New insights about the basic structure of the virus, how its replication is controlled, and how it destroys certain target cells may prove crucial to the eventual discovery of effective agents for the prevention and treatment of AIDS. At the same time, a

new approach to cancer treatment using interleukin-2 to activate the immune system to destroy cancer cells has been developed. Gains against genetic diseases are being made. A genetic marker for cystic fibrosis has been found, bringing scientists closer to identifying the gene itself and to discovering the basic defect causing this fatal inherited disease. Great strides are also being made in dealing with the complications of diabetes. One treatment approach, the transplantation of donor pancreas islet cells is progressing rapidly and offers great hope of providing recipients with a close facsimile of the normal functioning of the pancreas.

To a large extent the advances in biomedical research today determine medical practice available tomorrow. From the results of research come the means of improving the quality of health care and, ultimately, of reducing its costs. Although certain technological advances initially appear to increase health care costs, improved modes of diagnosis, treatment, and prevention eventually yield an overwhelming return on the research investment. Recent advances such as drug treatment rather than surgery for patent ductus arteriosus (a serious heart defect of infants), drug treatment of coronary artery disease instead of coronary bypass surgery in certain patients, and newly developed laser treatment for serious eye disease will significantly reduce costs associated with dealing with these health problems.

### **Recent Advances and Scientific Opportunities**

Biomedical research is moving forward at an unprecedented pace. Key discoveries in molecular biology, genetics, and immunology have led to the widespread use of techniques that are enabling scientists to address fundamental questions about the nature of living organisms. It is now possible to alter protein activity, to isolate components in developmental processes, or to repair defective enzyme functions using recombinant DNA and protein engineering techniques. Cells and bacteria can be transformed into factories to produce custom-



*A computer-generated view down the DNA double helix.*

made monoclonal antibodies or valuable hormones and growth factors. It is also significant that many of these discoveries were made possible through applying information and experience gained in one scientific discipline to problems in another.

These advances, which were made in the past decade, are still diffusing into existing fields of investigation. Questions that went unanswered for lack of appropriate technology are now under attack. Their solutions will accelerate our progress against disease, as well as raise new questions to explore.

This Report offers some examples of recent advances and opportunities for future progress in biomedical research. Programs sponsored by NIH encompass the entire spectrum of human disease and have led to numerous achievements in diagnosis, treatment, prevention, and understanding of the physiologic processes underlying disease states. The selections described here are not intended to provide a comprehensive listing of contributions NIH has made toward improving the health of the Nation, but rather to illustrate the scope of the research effort. This includes scientific disciplines that transcend Institute boundaries such as molecular

biology, structural biology, genetics, immunology, neurobiology, and endocrinology. Also included are two specific research initiatives, one on AIDS, and the other on a relatively recent topic, space medicine, both of which incorporate the work of a number of Institutes.

#### *Molecular Biology*

The biologist of decades ago was dependent on the microscope and dissecting instruments to examine the structure and function of physiologic systems within whole organisms. Today's investigator is able to develop an intimate understanding of biological pathways through the inspection and manipulation of the very molecules that compose those systems. Many of the questions that awaited the development of modern technology involve the genes that instruct the cells to produce the peptides used as fuel or as messengers to other cells, the enzymes that catalyze chemical reactions, or the structural proteins for support and locomotion of the organism.

Much of the knowledge employed by molecular biologists around the world stems from fundamental research carried out during the 1960's at NIH. Although it was known that the genetic material passed from one generation to the next was carried on chromosomes, the key to making this information

useful was the breaking of the genetic code—the system by which deoxyribonucleic acid (DNA) designates the proteins that are produced in the cell.

The discovery of bacterial enzymes that allow scientists to cut and splice genes has made it possible to "map" and to sequence DNA, to create it synthetically, and to determine which fragments code for desired proteins or control their production.

#### • *Site-Directed Mutagenesis.*

Recently, identification of specific sites of expression of particular genes has permitted researchers to alter these genes, using a method called "site-directed mutagenesis." This technique first involves determining the sequence of the nucleotide building blocks of the gene being studied. Next, copies of these sequences are synthesized in the laboratory, and a small fragment of each copy is altered to cause a change, or mutation, at a specific site. These altered sequences are then combined with the host DNA, using recombinant DNA technology. This technique replaces a normally occurring genetic instruction with another one that is man-made. The new instruction may be designed to produce a specific protein which geneticists can tailor to particular requirements; for example, for the production of antiviral or anticancer agents. In addition, site-directed mutagenesis has been used extensively by biophysicists to test theories concerning the relationship of a particular protein's structure to its function. If a mutation is produced at a single site on the gene coding for a protein, an altered protein may be produced. Biophysicists



*NIH intramural scientist examining stained fragments of DNA.*



thus can determine the relation of the altered protein structure to abnormal function; for example, the abnormal hemoglobin present in sickle cell disease or thalassemia.

#### *Structural Biology*

Frequently, the greatest strides are taken when technology developed in one field of research can be applied to answer questions in another field. Such is the case in structural biology where the theories and methods for studying physical properties of complex molecules (macromolecules) have been applied to biological problems. The result has been a dramatic expansion in the body of knowledge concerning the relationship of specific physiologic functions of macromolecules to their three-dimensional structures.

The implications of these newly-developed visual aids range from the rational design of drugs based upon their ability to fit the target receptor on a cell membrane much as a key fits a lock, to a new strategy for treating viral infections such as HTLV-III/LAV (responsible for AIDS) and rhinovirus (responsible for the common cold). Efforts are being made to enhance structural studies so that analyses of molecules will proceed more quickly, will achieve better resolution, and will accommodate a greater range of molecular sizes.

Technological advances in areas such as x-ray crystallography and nuclear magnetic resonance provide new opportunities to investigate the structural properties of physiologically active molecules.

• *X-Ray Crystallography.* Results obtained from x-ray crystallography during the last 2 years on the structure of four different proteins have revealed important common features of protein structure. These studies, however, denote only a beginning since these proteins are merely a representative sample of the large number of important protein structures. Recently, investigators have determined the complete, three-dimensional architecture of a common cold virus (rhinovirus) using x-ray crystallography employing a high energy synchrotron source. Scientists have long known

the general shape of the cold virus which, under the electron microscope, shows an outer wall composed of 20 triangles that fit together to form the geometric shape known as an icosahedron. Inside the hollow protein shell is the genetic material which, when released, directs the cell to replicate the virus.

The new studies provide a stereo view of the exact position of the molecules making up the protein structure, showing that each triangle of the protein shell has peaks and valleys formed by the irregular shape of protein molecules making up the shell. The part of the shell that must attach to a cell to cause infection lies within a deep cleft or "canyon" on each of the 20 triangular sides and appears to be too narrow for antibodies to reach. However, this finding raises the possibility that a molecule could be synthesized which would be small enough to enter the canyon and bind to the attachment site, preventing attachment of the virus to the cell and, consequently, preventing infection.

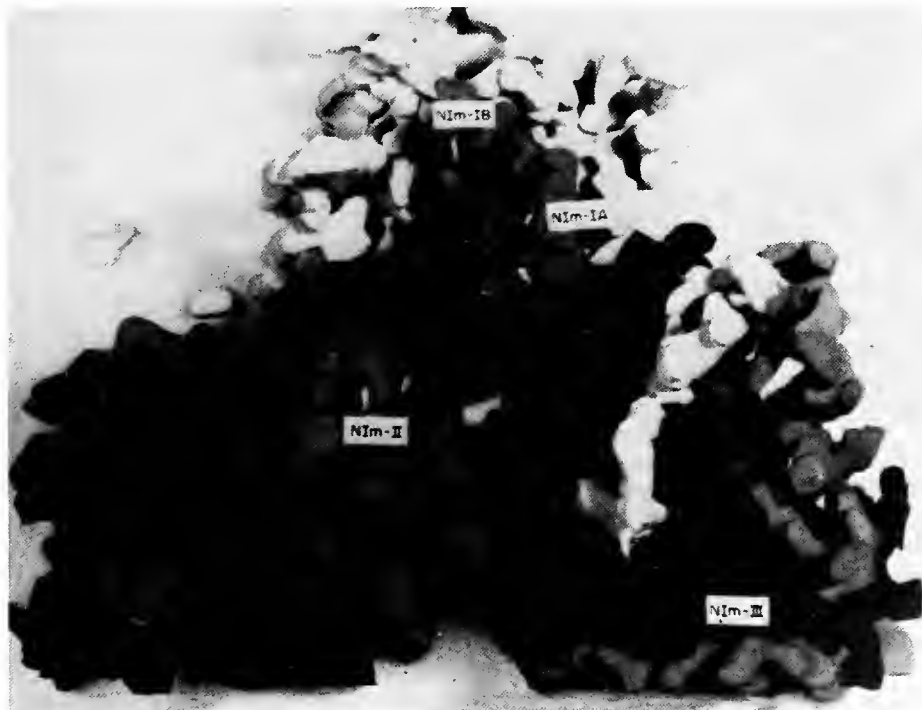
• *Nuclear Magnetic Resonance.* One of the most revealing and

rapidly evolving research tools now being used by molecular biologists is nuclear magnetic resonance. This technique measures the degree to which atomic nuclei within molecules absorb energy in magnetic fields and uses these measurements to make structural determinations. Using this technique, it is possible to determine the chemical composition of biologically important molecules, the length and nature of the bonds holding the atoms of the molecule together, and the three-dimensional arrangement of those atoms.

A significant advantage of this technique is that studies can now be performed on molecules in their typical physiologically active state; that is, either within the living organism or in aqueous solution, rather than in an unnatural solid state, such as in the crystalline state. Nuclear magnetic resonance is also being used to produce images of human subjects that are similar to those produced by x-ray computed tomography (CT).

#### *Genetics*

In conjunction with the advances in their ability to analyze genetic material that were described earlier,



*Model of a rhinovirus developed using x-ray crystallography enhanced by a high energy synchrotron source.*

scientists have recently attained an increased comprehension of the previously unknown genetic components of a number of diseases. For example, a predisposition to hypertension, atherosclerosis, and some forms of cancer may be inherited, as well as an increased vulnerability to environmental factors that influence the incidence of many disease states.

The result has been an intensified effort in the field of genetics to prepare for the advent of technological achievements that are visible on the horizon. Of the more than 3,000 genetic disorders, many are the result of a defect in only a single gene. These will be the most likely candidates for treatment by gene therapy and are thus the subject of rigorous investigation by several research teams.

Other groups are involved in the expansion of the arsenal of tools that permit analysis of the genome of individuals affected by genetic disorders. Examples of the new technologies as well as their current and future applications are described here.

- **Genetic Mapping.** Genes that code for particular proteins can be located on a chromosome by means of a DNA probe, or segment of complementary DNA, which was previously identified and localized. This mapping technique is facilitated by the increasing availability of well-characterized DNA probes.

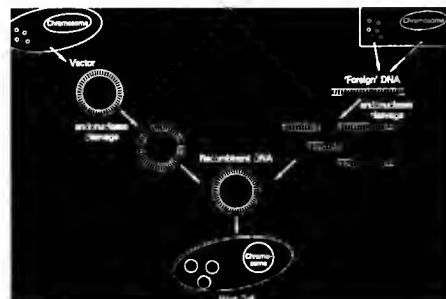
- **DNA Repository.** To foster genetic research, the NIH recently established a repository in which DNA segments will be collected, stored, and distributed to scientists around the world. The repository will eventually store copies of most of the 100,000 human genes and will enable scientists to locate and easily acquire the pieces of human DNA they need to locate genes on specific chromosomes, distinguish normal from abnormal genes, insert genes into chromosomes, and eventually treat genetic diseases.

The value of DNA probes in clinical research has been demonstrated also in studies of sickle cell anemia, Duchenne's muscular dystrophy, and thalassemia, which can now be identified before birth, using DNA



*Human chromosome-specific libraries are diluted and dispensed into individual user vials prior to freezing in liquid nitrogen for storage. (above)*

*A piece of DNA coding for a desired protein, such as insulin, can be cleaved from its source and inserted into the genome of a host, where DNA transcription results in the production of the same protein. (right)*



from cells obtained by amniocentesis to study DNA sequences and identify the mutation causing this disease.

- **Genetic Disorders.** Birth defects and genetic disorders are major contributors to infant mortality and lifelong morbidity but have been unusually difficult to approach experimentally. This situation is now changing due to the new research tools provided by molecular biology, and this field has become one of the most exciting and promising for research. Scientists are now studying, at the level of gene structure and expression, the basic processes involved at the earliest stages of development that determine proper or improper organ and limb formation. New techniques are also being developed and refined that could permit the insertion of new genes into cells with gene defects, and to

control their action correctly. Such research may lead eventually to human gene therapy. Gene therapy provides the opportunity to cure inherited diseases such as hemophilia or diabetes, rather than simply treating their symptoms.

- **Localization of the Cystic Fibrosis Gene.** Recently, progress has been reported in mapping the gene for cystic fibrosis (CF), the most common lethal childhood disease among white Americans. Using a DNA probe (called 917), investigators have identified a region on human chromosomal DNA that is closely associated with the occurrence of CF. This research, and related work, opens up the possibility of isolating the gene and the gene product. Then the nature of the genetic defect would become apparent, permitting the development of more rational treatment or prevention strategies.

- **Production of Factor VIII.** Blood coagulation factor VIII, which is absent or defective in the approximately 12,000 people in the United States who suffer from hemophilia A, must be replaced to control this bleeding disorder. Until recently, spontaneous bleeding in these patients, and bleeding during surgical or dental procedures, could only be controlled by replacing the missing blood factor by transfusion. Unfortunately, this essential therapy carries with it the risk of exposure to bloodborne viral diseases.

Recombinant DNA technology has recently been successfully applied to the synthetic production of factor VIII, and the product has been shown to be biologically active. This achievement marks the cloning of the largest, most complex protein produced through genetic engineering. Although it may require several years to develop and clinically test this product, the achievement of a laboratory-produced clotting factor is of great importance because it should lead to a less hazardous and a less costly alternative to plasma-derived factor VIII.

- **Color Vision.** An exciting new finding concerning the genetics of color vision was recently announced. These scientists sequenced the genes that code for components of the retinal pigments necessary to induce the neural signals that produce color vision. With this tool, they were able to analyze the molecular details of gene structures in normal and color-blind individuals and to deduce the genetic basis for color blindness or color vision.

#### *Immunology*

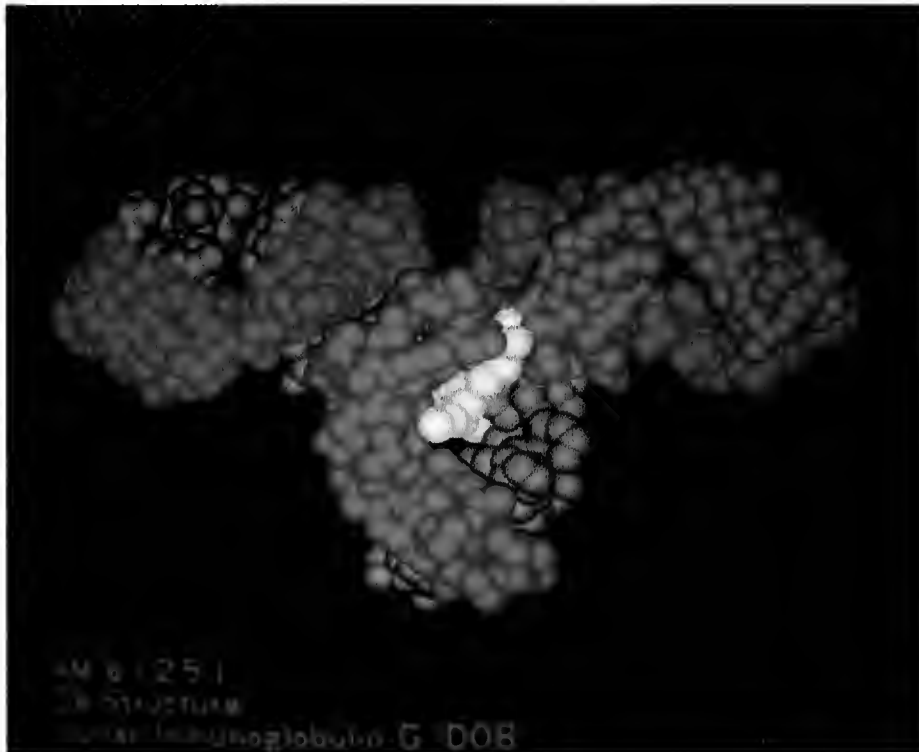
Basic studies in immunology such as the characterization of the immunoglobulin molecule and the different cell types that make up the immune system have led to the development of important techniques that are used in all aspects of biomedical research.

- **Monoclonal Antibodies.** Foremost among these techniques is the ability to fuse two cell types, one an antibody-producing B-cell with a myeloma (cancer) cell which may be kept alive indefinitely in cell culture. The resulting hybridoma

will manufacture highly specific antibody for any number of uses. The NIH has established a monoclonal antibody bank to develop new antibodies and to make published antibodies available to investigators for research purposes. Recombinant DNA techniques and monoclonal antibody technologies hold enormous promise for use in rapidly diagnosing and characterizing tumors and for treating patients, as well as to pursue developmental studies (i.e., limb development). For instance, monoclonal antibodies, designed specifically to find cancer cells, are being applied directly to biopsy samples to aid in tumor characterization. This technique is particularly important when dealing with a form of cancer that responds only to a certain treatment but is difficult to distinguish from other tumors using traditional diagnostic methods. These antibodies, which can be tagged with radioactive tracers, are also showing promise in clinical studies to detect the extent of disease (including hidden metastases) in patients with colon and other cancers.

- **Immune Regulation.** The immune system consists of many different cell populations, each performing separate functions but interacting within a wholly integrated system. Investigators are cloning and culturing these cells in quantity to facilitate detailed studies of the genes that control cell functions. At least three distinct steps have been identified as necessary for B-cell activation, proliferation, and differentiation and are induced by different molecular signals originating from separate cellular components of the immune system. The identification of different activation signals raises the possibility of developing varied means to regulate cell functions externally to combat disease.

- **Genetic Engineering and Vaccines.** The cloning and sequencing of genes that code for the proteins of pathogenic organisms are extremely important in the development of genetically engineered vaccines, composed of purified products that induce protective immunity in the absence of toxic side effects. In addition, a number of



Scientists have developed a computer graphics system demonstrated here with a computer-generated space-filling model of an immunoglobulin molecule (IgG) where smooth spheres depict the surfaces of the molecule's atoms, giving a three-dimensional effect.

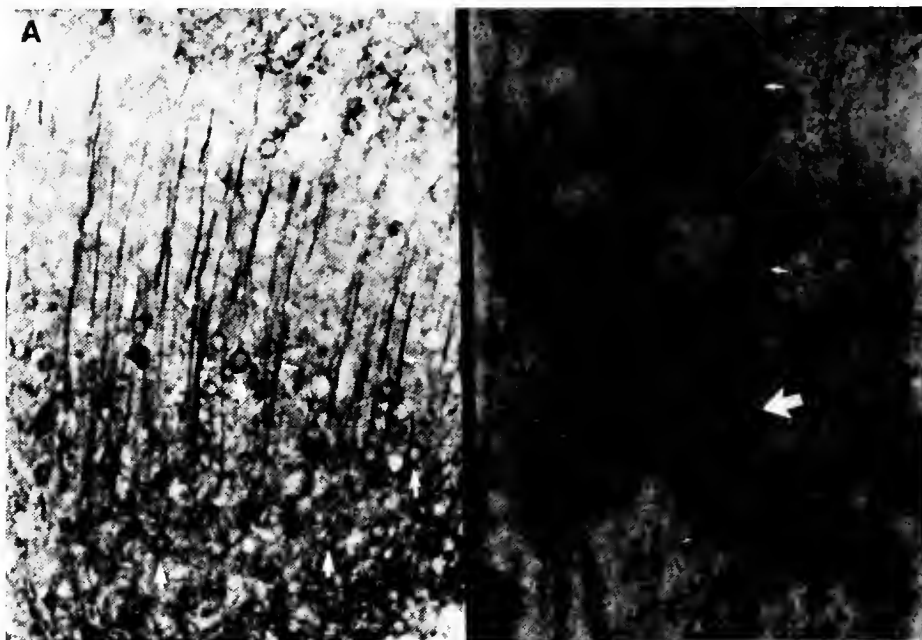
acellular candidate pertussis vaccines, made by extracting appropriate antigens from the whole cell, are being developed and tested with NIH support. This testing includes a large-scale efficacy trial in Sweden, where pertussis is common and vaccination rates are low.

Recent advances in applying the techniques of molecular biology have led to an important breakthrough in the development of vaccines against influenza. A hybrid human influenza virus was constructed using two genes derived from a human influenza virus combined with six other genes (necessary for virus growth) derived from a harmless avian influenza virus. The hybrid virus was safe and non-transmissible in adult volunteers. This live virus vaccine can be administered as nose drops, which deliver it to the tissues first infected by disease-causing strains. A second benefit is that live virus vaccines generally produce better protection than inactivated ones. Further clinical studies of this vaccine, developed in an NIH intramural laboratory, are under way.

Until now, progress in treating and preventing respiratory syncytial



*An inexpensive, convenient to store, acellular typhus vaccine is being field-tested in Nepal where this disease is a major public health problem.*



*A. Detection by antibody of the calcium-regulated enzyme, cyclic AMP phosphodiesterase, in specific nerve cells (pyramidal cells) of the cerebral cortex. (left)*

*B. A single pyramidal cell at high magnification shows intense staining of the cell body (large arrow) and of the dendrites (small arrows), indicating the presence of enzyme in these regions. The presence of enzyme in the dendrites is in keeping with its essential role in neurotransmission. (right)*

(RS) virus, a virus that causes serious respiratory disease in children, has been frustratingly slow due to difficulties inherent in its cultivation and purification. Investigators have succeeded in characterizing and mapping the genome (the complete set of hereditary factors) of RS virus. Research has provided the first description of the inner workings of this important virus and gives renewed impetus for vaccine and antiviral drug development.

#### *Neurobiology*

The human nervous system, awesome in its intricacy and capabilities, has for centuries remained an intractable biological enigma. The scope of problems inherent in studying the central nervous system is staggering. Within the brain alone, there may be 100 billion nerve cells (neurons), perhaps as many as 1,000 billion. Each one of these cells is interconnected with other neurons. The number of these connections may well be in excess of 100 trillion. By comparison, the

brain towers above the largest electronic computer in terms of complexity.

Like all other cells in the human body, brain cells contain genetic information coding for all the peptides necessary for life. Investigators have succeeded in identifying the cellular and chromosomal locations of several of the more than 30,000 genes that control the production of these proteins, and have also produced important new evidence regarding the functions of some of these proteins in the transfer of information within the human. These studies are of vital importance in understanding the action of the normal brain, as well as in the treatment of neurological disorders such as pre-senile dementia and Huntington's disease.

• *Basic Studies.* Studies in animals have shown that fetal nervous tissue can be implanted in the brain and will survive and perform vital secretory functions. Synaptic connections have been observed between host and implanted tissue. This experimental work will become

increasingly significant in the study of hormone and neurotransmitter deficiency disorders and specific degenerative consequences of such disorders as Parkinson's disease.

Researchers have discovered important new information on the role of "gap junctions" that exist between cells. Such gap junctions are important in intercellular communications that affect development. This finding is of great potential significance to investigators seeking to understand the causes of developmental abnormalities; e.g., the failure of an eye to form or the gross underdevelopment of one side of the brain.

A disorder strikingly similar to Parkinson's disease can be induced experimentally by injection of a neurotoxin. This drug causes nerve cell degeneration in a region of the brain involved in motor coordination, which results in the typical motor dysfunction associated with Parkinson's disease. The condition closely mimics the disease and provides an important animal model for research.

- *Epilepsy.* Scientists are exploring such new experimental diagnostic techniques as magnetoencephalography (MEG) to pinpoint the exact brain abnormality responsible for epilepsy. The cells in the nervous system maintain an electrical potential across their outer membranes resulting in magnetic fields which can be measured by this new method. The measurement of extracranial magnetic fields produced by an abnormal discharge in one part of the human brain may be able to provide precise information about the location, depth, and orientation of currents within the epileptogenic focus. Use of MEG offers a new and more precise methodology to study the electrical activity in the brain.

New epilepsy treatments are also emerging. Barbiturates have long been an important part of antiepilepsy drug therapy; however, serious side effects with these compounds have become more apparent. New surgical techniques are beginning to help those epilepsy patients whose seizures have not been controlled

by drugs. With modern imaging techniques physicians are able to perform microsurgery and excise even the tiniest lesion responsible for the abnormal discharges of epilepsy.

- *Neurogenetics.* One of the most exciting emerging areas of research is basic neurogenetics, the study of the genetic basis by which organisms respond to stimuli. These neurological processes include learning, sensory perception, and simple reflex actions. A large portion of the genetic endowment of all animals seems to deal with these brain functions. This has been determined by the diversity of messenger RNA manufactured in the brain, when compared to that in other tissues. Researchers are now exploring how genetic techniques such as recombinant DNA technology may be harnessed to develop a better understanding of the complexities of brain function at the cellular and molecular levels. One direct method involves exploration of the manner in which the electrical signals of the brain are translated into the chemical signals of the endocrine system that control vital metabolic functions as well as appetite stimulation and suppression.

- *Alzheimer Disease.* Several families characterized by a high incidence of familial Alzheimer disease have been identified, and cells from known patients, at-risk family members, and unaffected

family members are now being banked in the Aging Cell Repository. The DNA from these families will be used to search for the chromosomal location(s) of genes responsible for this form of the disease.

### *Endocrinology*

- *Application of Biotechnology to the Synthesis of Hormones.* The development of powerful recombinant DNA methods coupled with other recent advances in molecular biology have resulted in a vast accumulation of knowledge about hormones. Prior to the application of these techniques, isolation of hormones involved laborious extraction and purification from large amounts of tissue. New recombinant DNA techniques have already made possible the synthesis of potentially unlimited amounts of clinically active insulin, somatostatin (a hormone responsible for regulating the secretion of other important hormones), and growth hormone. The capability exists to isolate, to characterize, and even to synthesize compounds which mimic or inhibit the action of hypothalamic releasing hormones (hormones originating in the brain that control the release of hormones in the pituitary) thus leading to opportunities to diagnose and treat hormone-dependent disorders—for example, endometriosis, polycystic ovarian disease, breast cancer, and precocious puberty.

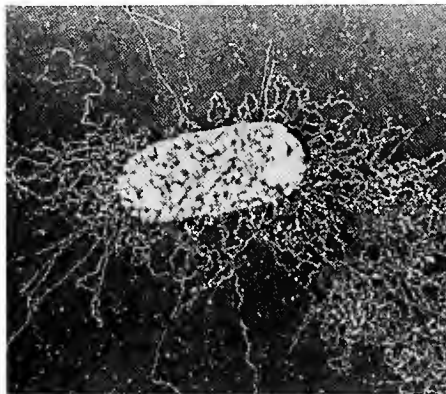
Exciting endocrinology research findings are paving the way for an array of potential new therapies as investigators identify, characterize, and synthesize new peptides. This knowledge has profound implications for comprehending the role of small proteins in control of the insulin-producing islet cells of the pancreas, in motility of the bowel, and in appetite and satiety. Results obtained from this research are being applied to a broad range of diseases including cancer, rheumatoid arthritis, and other conditions.

- *Regulatory Role of Receptors.* Advances in the field of endocrinology have resulted in a great leap in our understanding of the regulatory role of cell receptors for hormones,



*Patient with Alzheimer disease being examined by her physician.*



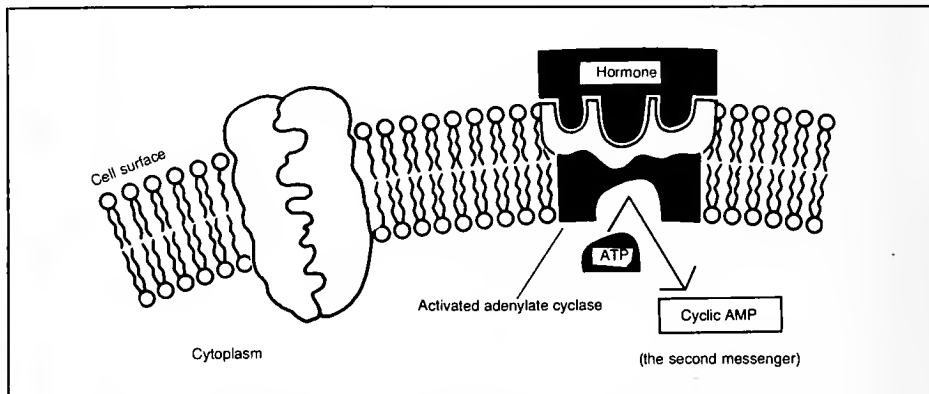


*Bacteria can be used as factories to produce biologically significant compounds.*

growth factors, antigens, neurotransmitters, and drugs. The availability of purified receptor molecules; cloned genes which encode these receptors; topographic visualization of tissue-specific receptors; and reagents to analyze the interaction between chemical signals, receptors, and target molecules, permits enhanced understanding and ability to alter the regulation of hormone action. This capability will likely lead to methods to control high blood pressure, immune function, neurotransmission, nutrient metabolism, fertility, and cell division.

- **New Therapies.** Remarkable progress has been made in understanding a variety of growth factors and in identifying those hormones essential to growth processes.

In many patients, growth hormone deficiency is due to a primary deficiency of hypothalamic growth hormone releasing factor (GRF)—a neuropeptide which stimulates the pituitary to produce and release growth hormone—rather than to a lack of growth hormone itself. Therefore, treatment with the releasing factor is useful for some children with hypopituitary short stature. NIH grantees have recently synthesized GRF, and clinical tests showed that it can achieve, in patients with a primary deficiency of this factor, an increase in growth comparable to that seen with growth hormone therapy. Also, it promises to be safer, less costly, and more easily administered.



*When a hormone binds to its specific receptor on a cell membrane, it activates an enzyme (adenylate cyclase) which then converts ATP into cyclic AMP, the messenger that sends a signal to the interior of the cell.*

Additionally, the recent observation that growth hormone release can be achieved with intranasal administration of GRF offers hope that this mode of delivery, rather than injections, may be feasible in the future.

Research on islet cell (insulin-secreting pancreatic cells) transplantation offers a potential means of restoring natural insulin-producing capacity to insulin-dependent diabetics and, consequently, holds considerable hope for juvenile diabetics and their families. Recent accomplishments in islet cell transplantation include: (1) the demonstration in animals that islet transplants will prevent, reverse, or arrest the early complications of diabetes involving the eyes, kidneys, and autonomic nervous system; (2) the development of methods to prevent rejection of isolated adult islets transplanted between different strains of animals as well as between different species (rat to mouse); and (3) the development of methods to separate and purify adult and fetal islet cells. Additional basic and clinical research is needed to determine whether human islet cell transplantation will prevent or arrest diabetic complications, to elucidate the immunology of preventing rejection in various types of tissues and organs, and to lay the groundwork for possible large-scale clinical studies of islet transplantation.

An array of potential new therapies is expected to emerge as

researchers characterize the physiologic roles in health and disease of other important hormones and determine their genetic blueprints.

#### *Acquired Immune Deficiency Syndrome (AIDS)*

Although there is still much to be learned about the biology and pathogenesis of AIDS and accompanying opportunistic infections, the rapid progress that has been made thus far in AIDS research is due in large part to the science base already developed through prior support of viral and immunologic basic research. For example the agent that causes AIDS, Human T-Lymphocyte Virus Type III/Lymphadenopathy-Associated Virus (HTLV-III/LAV),\* has many novel genes, one of which makes a product which some researchers believe accelerates the reading of other viral genes as well as activation of cellular genes. This may be the method by which the virus kills an activated target T-cell.

NIH continues to actively support basic research in such areas as viral latency, incorporation of the viral genome in the host cell, the identification of markers for predicting occurrence of disease in high-risk individuals, genetic variation among HTLV-III/LAV isolates, opportunistic infections, and immunologic defects.

\* The name human immunodeficiency virus (HIV) has also been proposed for these viruses. (Science 1986: 232:697)

• *Epidemiology and Natural History.* Epidemiologic studies of AIDS transmission within and among risk groups are essential to predicting the potential future spread of the disease. New epidemiologic data are leading to a clearer understanding of how the virus can be transmitted and what happens to the infected individual. It is known that HTLV-III/LAV can be transmitted by heterosexual as well as homosexual practices, by transfusion of blood or its components, and from infected mother to child during birth. In at least two countries, there has been a significant shift from mostly male AIDS cases in the past, to a current high of 50 percent female AIDS patients.

• *Development and Testing of Drugs for the Treatment of HTLV-III/LAV and Opportunistic Infections.* Major efforts are currently under way to evaluate antiviral agents in AIDS and AIDS-related complex (ARC) patients. Immunomodulators such as interferon and interleukin-2, as well as procedures such as bone marrow transplantation between identical twins, are being studied in attempts to reconstitute the damaged immune system in AIDS patients.

Recently, a major collaborative program under the auspices of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI) has been initiated to develop, screen,

and test promising agents for the treatment of AIDS, ARC, and opportunistic infections. The drug development phase of the program includes the acquisition, screening, selection, formulation, production, and toxicological testing of prospective antiviral drugs.

Phase I and II clinical trials of candidate anti-HTLV-III/LAV immunomodulators, immune enhancement agents, and agents for the treatment of opportunistic infections are being conducted in the NIH intramural program and at a number of AIDS Treatment Evaluation Units.

Because AIDS is characterized by general suppression of the immune system, patients are subject to numerous infections which would not cause serious illness in otherwise healthy persons. These opportunistic infections span a broad spectrum of conditions affecting various organ systems and physiologic processes, hence, most NIH research institutes and divisions are involved in this research effort.

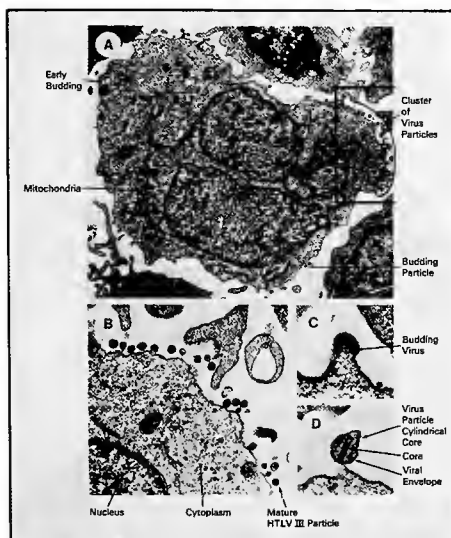
• *AIDS Vaccine Development and Testing.* All known methodologies of vaccine development and production will be attempted to produce an effective AIDS vaccine. These will include extracting candidate proteins from large-scale production of virus, identifying appropriate antigens and synthesizing them, inserting appropriate genomes in bacteria or yeast for antigen production, constructing sequence specific peptides of selected regions of the viral envelope, and inserting appropriate HTLV-III/LAV genome segments into vector viruses, and isolating immune globulin from individuals with neutralizing antibodies. While efforts to develop a vaccine are intensifying, there are formidable problems in this area. Retroviruses have special features which would tend to obviate some basic effective vaccine approaches, such as the use of inactive virus and nonpathogenic variants.

Another potential problem is tied to the observation that different HTLV-III/LAV virus isolates tend to vary significantly in their genetic

material, which suggests that either a number of antigenic types may exist, or that the viral antigenicity may readily change. In either case, the vaccine inoculum may have to be complex.

• *AIDS Outreach/Information Activities.* Advances in AIDS research must, of course, be transmitted to the public. NIH supports an AIDS outreach program that has held a series of conferences throughout the United States aimed primarily at health care professionals and public service personnel. These conferences have been very successful and in all cases have been oversubscribed.

The NIH has expanded the computerized Physicians Data Query (PDQ) system, developed collaboratively by the National Cancer Institute and the National Library of Medicine for the dissemination of information on cancer chemotherapy and clinical trials, to include analogous information on AIDS therapy.



*Replication of HTLV-III/LAV.*



*Astronauts Gerald P. Carr (left) and Edward G. Gibson (floating) are shown in the forward experiment area demonstrating zero-g effects on weights. The Skylab 4 crewmen lived in the weightless environment for a total of 84 days.*

### *Space Medicine*

A growing need exists to begin now to anticipate the health needs created by the space program and possible future applications of this activity. Data collected during space flights have demonstrated that humans and other animals undergo profound physiological changes as a result of the microgravity environment that exists in space.

• **Cardiovascular Effects.** One immediate effect of microgravity on the cardiovascular system is seen in the incidence of post-flight orthostatic intolerance (microgravity-induced changes in the cardiovascular system that can cause fainting or dizziness and difficulty in maintaining an upright posture when gravity is reimposed during reentry and landing). Initial results suggest that although the cardiovascular system can adjust fairly quickly to fluid shift and blood volume loss early in space flight, the long-term adaptation of the cardiovascular system will require extensive additional investigation.

• **Space Motion Sickness.** One of the most obvious and bothersome physiological problems engendered by space travel is space motion sickness, a neurophysiological problem resulting from conflicting signals sent by the balancing organs of the inner ear, the eyes, and the muscle sensors. It appears that during flight all signals from the organ in the inner ear that senses gravity and linear acceleration come to be interpreted by the brain as linear motion. About half of all space crews experience lethargy and vomiting for 3 or 4 days after initial entry into weightlessness. Before measures can be taken to reduce or prevent motion sickness in space, much more must be known about the underlying neurophysiological mechanisms.

• **Radiation Hazards.** The radiation hazard posed by space travel could conceivably constitute one of the more limiting factors on long-term manned space missions. Additional studies of the biophysics of radiation-induced cancer are needed to assist in the establishment of radiation protection standards for occupational exposures on earth as well as in space. Understanding the health effects of radiation in space, however, will be made more difficult because of the effect that space flight has on normal cell physiology. Recent studies have shown, for instance, that the ability of immune-competent cells to recognize and respond to foreign substances is generally depressed during space flight. These findings suggest the

need for additional studies since the cells involved in the immune response are responsible for both protection against infectious agents and for immune surveillance against harmful cell growth—such as radiation-induced cancer.

• **Research in Space.** The novel environment encountered in space also provides a “laboratory” in which studies and procedures can be performed which would be exceedingly difficult or impossible to achieve on the earth’s surface. For instance,

—Protein crystallography is an important technique in determining protein structure and function, knowledge of which may enable scientists to understand the causes of molecular malfunctioning which can lead to cancer and other diseases. Growing protein crystals in a gravity-free environment should produce larger crystals with fewer imperfections, characteristics that are helpful to researchers using x-ray diffraction equipment.

—Many important biological materials—cells, enzymes, and hormones—are currently being separated and purified by electrophoresis, but because earth’s gravity exerts a negative influence on the separation process, only minute amounts can be extracted at one time. Processing in gravity-free space offers a means of separating biologicals in the large quantities and high levels of purity needed for research, clinical testing, and pharmaceutical production.

These examples illustrate both recent achievements and future opportunities that will enhance our understanding of disease processes.

### **NIH-Wide Policy Issues**

The NIH continues to assess its role as a health agency and as the principal source of support for biomedical research. Significant science policy issues must be examined by the NIH as research findings advance. In addressing policy issues, the NIH utilizes the advice of the Advisory Committee to the Director, NIH, as part of the policy develop-

ment process. This section of the Report examines a number of policy issues currently being addressed by the NIH, namely, the extramural research infrastructure, NIH construction, improving the extramural awards process, biotechnology, and the care and use of animals in research.

### **Extramural Research Infrastructure**

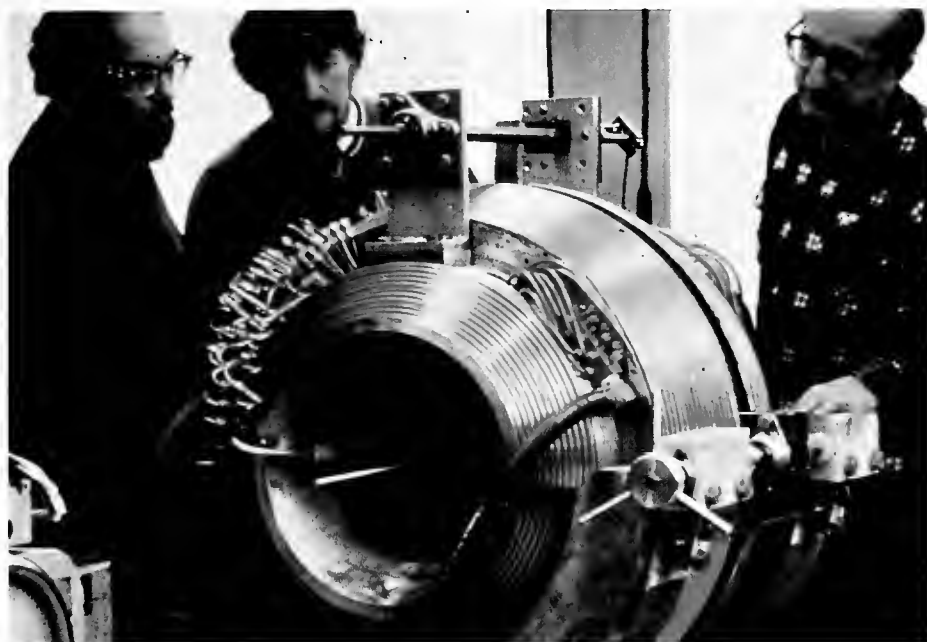
The conduct of biomedical research is critically dependent upon a strong institutional research infrastructure. This infrastructure includes modern research instrumentation, facilities, and the research talent necessary to respond to a vast array of scientific opportunities. In recent attempts to strengthen the university research base, the NIH continues to address (1) the issue of increasing shortages and obsolescence of research instrumentation; (2) the need for construction and upgrading of extramural research facilities; and (3) the need for training research manpower.

### **Research Instrumentation**

During the past decade, leaders in the extramural research community, the Congress, and the Administration have expressed increasing concern over the state of research instrumentation. This concern is related to the fact that biomedical research has become progressively more equipment-intensive and that instruments have become increasingly complex and costly. Although the NIH has recently strengthened its support of research instruments, serious problems still remain, particularly the provision of smaller pieces of equipment and the maintenance and repair of current inventories.

The NIH currently has in place a variety of mechanisms for the support of research instrumentation. Individual research project grant awards are the principal source of support for the purchase of laboratory equipment. The Division of Research Resources (DRR), through the Shared Biomedical Research Instrumentation Program, provides support for the acquisition of large-scale instrumentation in the \$100,000 to \$300,000 cost range. The DRR





*NIH engineers working on the fabrication of the nuclear magnetic resonance imaging device.*

also provides advanced instrumentation on a regional and national basis at biomedical research technology centers through the Biomedical Research Technology Program. In addition, instrumentation support is provided through the Minority Biomedical Research Support Program. The NIH estimates that in FY 1985 it awarded \$144 million, or approximately 4.2 percent of a \$3.4 billion research award base, for research instruments.

In a recent NIH-funded survey of instrumentation needs in biological science departments in universities and medical schools, it was found that existing mechanisms are meeting the need for large equipment with a purchase price in excess of \$100,000; however, a serious shortfall exists in the provision of smaller pieces of equipment in the \$5,000 to \$60,000 range. A report of this survey, "Academic Research Equipment and Equipment Needs in the Biological and Medical Sciences," was published in April 1985.

The survey findings served as background for the December 1985 meeting of the Advisory Committee to the Director, NIH, where issues in this area were discussed. The

Committee confirmed that the need for support is greatest for smaller pieces of equipment and that maintenance and repair of current instruments is a serious and growing problem. The Committee also favored keeping all current NIH instrumentation support mechanisms active and funded to the extent possible and supported the view that the traditional individual research project grant should be used as a principal vehicle for requesting equipment support. The Committee acknowledged that research progress in some cases is being impeded because of equipment shortages but recognized that under current budget limitations increased support for instruments would require reductions in other areas.

#### *Extramural Health Research Facilities*

The NIH first supported construction of extramural health research facilities in 1948, when appropriations were made to the National Cancer Institute. During the 38-year period since then, the NIH has had available a variety of authorities for construction of health research facilities and has spent approximately \$950 million for such purposes. All but one of the authorities have been for relatively specific pur-

poses, the one exception being the Health Research Facilities Act of 1956 which provided a broader and more general authority for the construction, renovation, and replacement of non-Federal health-related research facilities with no limitation as to area of health-related research or type of facility. Since funds for the Health Research Facilities program ran out in 1972, approximately \$255 million has been obligated for construction. Nearly all of these funds have been for the construction and renovation of cancer research facilities.

Efforts are under way to establish the requirements for construction and renovation of extramural facilities. The NIH initiated efforts to conduct a comprehensive survey of the needs and status of biomedical research facilities. A pretest has been completed in which a wide spectrum of institutions were sampled. The nature of problems relevant to facilities and the extent of repair and replacement needs are significant; however, they vary considerably among universities, hospitals, and nonprofit institutions. Since the National Science Foundation Authorization Act for FY 1986 authorizes and directs the NSF to design, establish, and maintain a permanent data collection and analysis capability to assess the research facilities needs of universities, the NSF will be initiating a survey which should give a clearer picture of extramural health research construction requirements.

At the same time that better measures of the need for extramural construction and renovation are being developed, the NIH will be exploring the possibility of proposing a new, general authority for extramural construction. Currently, only the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Eye Institute have authority for the construction of extramural facilities.

#### *Research Training*

A critical mass of well-trained scientists is essential to the maintenance of a strong research infrastructure. The National Institutes of Health is therefore committed to attracting the best candidates to biomedical



*NIH grantee and students discuss research findings.*

research training programs. The December 1983 meeting of the Advisory Committee to the Director, NIH, was devoted to discussion of trends in research support for manpower development, determination of needs in the area, preparation of successful investigators, and an appropriate mix of training programs.

The National Research Service Award (NRSA) Act, enacted in 1974, abolished and consolidated previous research training authorities under the PHS Act. The NRSA is the only authority under which the NIH supports the basic preparation of individuals for a career in biomedical and behavioral research. Through a system of individual fellowships and institutional training grants, the trainee or fellow receives a stipend for full-time concentrated study with a particular research focus.

Under the NRSA Act, the National Academy of Sciences (NAS) is charged with conducting a continuing study of the national needs for biomedical and behavioral research personnel. Reports from this study are published periodically and, while they do not take into account the increasing needs of private industry, they do provide a useful starting point for estimating research manpower needs and indi-

cate a minimum level required to keep the supply of investigators in balance with the Institutes' basic program needs.

From FY 1980 through FY 1985, the number of NIH-supported full-time research training positions under the NRSA has fluctuated between about 10,700 and 10,400. These numbers have been relatively consistent with the NAS recommendations. In FY 1986 the NIH supported approximately 10,370 full-time research training positions and estimates supporting 10,867 in FY 1987.

The NAS has increased the total number of positions it recommends for support in 1988-89. The NIH estimates its share of the NAS recommendations for these years to be 10,037 for 1988, 11,436 for 1989, and 12,103 for 1990. The NAS has also found that clinical faculties in medical schools have continued to expand, and more newly hired clinical faculty should have some research training if the schools are to maintain their clinical research capacity. Thus, the NAS has recommended that the number of traineeships and fellowships in the clinical sciences gradually be increased from the current levels of less than 2,400 to 3,000 by 1990.

The NIH has sought to provide

adequate stipend levels to attract high caliber applicants. The Congress added funds in FY 1985 to provide a stipend increase so that NIH stipend levels would be more comparable to those paid by other agencies. For postdoctoral trainees, stipend levels were adjusted to achieve a closer parity to medical house staff salaries at U.S. teaching hospitals. Nevertheless, the incentive for stimulating interest in research careers may be somewhat diminished by maintaining the NRSA stipends over the next 2 years at the same FY 1985 level.

The Physician Scientists Award Program, launched in 1984, encourages newly trained physicians to develop independent research skills and experience in a fundamental science. The NIH funded approximately 37 individual and three institutional physician scientists awards in FY 1984 and approximately 96 individual and nine institutional awards in FY 1985.

### **National Institutes of Health Construction**

The NIH laboratories and offices are located on a 311-acre campus in Bethesda, Maryland, with other facilities in Research Triangle Park, North Carolina; Baltimore and Frederick, Maryland; and Hamilton, Montana. Physical facilities on the Bethesda campus include about 50 separate buildings and a substantial support system. The NIH is carrying out a long-range program of improvements to eliminate functional obsolescence and to maintain the facilities at a suitable level for conducting modern biomedical research. New construction has been limited within the last few years. The NIH is, however, carrying out three major multi-year construction projects on the NIH campus. These are the modernization of the Clinical Center, the renovation of laboratory buildings, and the upgrading of animal facilities.

### **Current Activities Under Way**

- *Clinical Center Modernization.* Since 1979 the NIH has been modernizing the Warren Grant Magnuson Clinical Center, a 500-bed research hospital and laboratory facility on the Bethesda campus.

This effort is in the 8th year of a projected 15-year schedule. Projects completed thus far include renovations of several patient care units, establishment of "areas of refuge" for protection against fire, development of a surgical intensive care unit, automation and upgrading of elevators, and renovation of space for clinical support activities, such as pharmacy and central sterile supply.

- *Upgrading of Animal Facilities.*

The NIH has set a goal of ensuring that all animal facilities on the NIH campus are accreditable by October 1987. Approximately 80 percent of NIH intramural animal holding space currently meets the standards of the American Association for Accreditation of Laboratory Animal Care (AAALAC). Implementation of the animal facilities initiative will proceed in two phases. The first phase, of a 2-year duration, would involve the consolidation of existing animal facilities within individual buildings, renovation of existing space, and new construction. The second phase, of a 5- to 10-year duration, would require the greater consolidation of scattered animal holding activities and construction of new facilities.

- *Additional Construction.*

Buildings recently completed or under construction on the Bethesda campus include an extension to a

building for handling radioactive and hazardous waste, an underground facility to accommodate two cyclotrons for production of short-lived radioisotopes needed for research using positron emission tomography, and an extension to another building to partially relieve overcrowding in the laboratories of the National Institute of Child Health and Human Development (NICHD). In addition, a program for renovation of six of the older laboratory buildings is under way to maintain the facilities at a suitable level to accommodate sophisticated technology for the conduct of modern biomedical research.

### **Improving the Extramural Awards Process**

The efficiency and effectiveness of the extramural awards system is an issue of continuing importance. The NIH has undertaken several initiatives to simplify its current policies and procedures to enhance the stability and productivity of principal investigators.

Approximately 2 years ago, the NIH undertook a thorough review of its policies governing the extramural awards system. Several areas of concern were identified over the course of this review: (1) the average project award period of 3 years placed first-time principal investigators at a disadvantage in competing for continued research grant sup-

port, (2) the award system failed to emphasize the "track record" of an established investigator as a criterion for review, and (3) the research grant application itself had become complex and lengthy.

The November 1984 meeting of the Advisory Committee to the Director, NIH, was devoted to a discussion of possible steps that could be taken to simplify the awards system in ways that would foster creativity in research. Actions taken as a followup to the meeting were directed primarily toward lengthening the period of awards for investigators and reducing requirements associated with the preparation and review of applications.

### *Increasing the Period of Support for Researchers*

- *First-time Investigators.* The First Independent Research Support and Transition Award (FIRST) Program was designed to provide new, independent biomedical investigators with adequate time to establish and nurture a research program before recompeting for continued support. Applications for FIRST awards will undergo traditional merit review.

The length of the FIRST award will be for a period of 5 years, allowing awardees sufficient time to develop research capabilities and to demonstrate the merit of their ideas. All awarding NIH Bureaus, Institutes, and Divisions are authorized to participate in the FIRST Program, and they may also utilize the traditional investigator-initiated research grant mechanism (ROI) for a similar purpose.

- *Well-Established Investigators.* The Method to Extend Research in Time Award (MERIT) Program was designed to recognize the unique strengths of well-established investigators by providing longer, more stable research grant support. The MERIT award will support investigators whose research competence is distinctly superior in order to foster their continued creativity and spare them some of the administrative burdens associated with preparation and submission of research grant applications. The MERIT award will be authorized for up to a 10-year period to be funded in two



*NIH Clinical Center and Ambulatory Care Research Facility.*

phases, the first for a period of 5 years. Request for an extension of up to an additional 5 years will be in the form of a progress report of achievements during the initial award.

#### *Improving Other Aspects of the Extramural Awards System*

In addition to initiatives relevant to tenure of awards, the NIH has undertaken other activities to make less burdensome the way in which the peer review system is applied. Changes in instructions regarding page limitation on research grant applications have been proposed in conjunction with OMB renewal of the use of the research grant application form. No major qualitative changes have been requested, but core elements common to all proposals will be limited in length. Enforcement of the new guidelines on page limitation will be accompanied by a major effort to acquaint NIH study section members with the new initiative and to assure research grant award applicants that shorter proposals will be reviewed fairly.

Other activities under discussion include improving the summary critiques of proposals and simplifying materials provided to council members. Consideration is also being given to the composition of peer review groups to assure the breadth and depth of experience necessary to judge proposals and to ways of providing a pool of prequalified individuals to be accorded full voting privileges when called in as special reviewers.

#### **Biotechnology**

New developments in biotechnology are based largely on the sustained support for basic research in molecular biology and immunology which has been provided by NIH over the past several decades. As is true of many major advances, the emergence of biotechnology has also created a new set of issues pertaining to public health, the environment, university and industry relationships, and national policies to enhance industrial competitiveness.

In examining the broad array of policy concerns, it became clear that

many are outside the purview and sphere of influence of NIH. To reach consensus about the most appropriate role the NIH might play in fostering the Nation's leadership in biotechnology, the June 1985 meeting of the Advisory Committee to the Director, NIH, was devoted exclusively to intense deliberation on the subject. Participants at the meeting included representatives of large and small biotechnology firms, pharmaceutical companies, instrument companies, universities, Federal departments and agencies, and private foundations.



*Over 200 firms, both large and small, are engaged in biotechnology research.*

From discussions at the June meeting, there emerged a clear consensus that the NIH can contribute best to the success of the U.S. biotechnology industry by sustaining its intensive support for basic research and research training in the underlying areas of molecular biology, genetics, and immunology. It may contribute further by emphasizing selectively, research and research training related to near-term commercial application (generic applied research). Consistent with the overall levels of funding available, the NIH intends to pursue initiatives in keeping with these themes.

Another result of the discussions at the Committee meeting was recognition of the need to exploit the strong biotechnology capability that exists in NIH intramural programs. Thus, NIH plans to encourage greater interaction between intramural scientists and industry and to increase the number of U.S. industrial scientists who pursue

research activities at NIH. To enlarge the role of the intramural laboratories in providing sound, basic research training in areas underlying biotechnology, the NIH has initiated a National Research Council-NIH Research Associateship Program in Biotechnology. Through this initiative promising scientists may increase their proficiency in biotechnology by working for a period of 1 to 3 years under the preceptorship of senior scientists in various NIH laboratories. In addition, the policy governing outside activities of NIH employees has been revised to permit scientists to consult for industry, subject to conditions which minimize the potential for conflict of interest and which limit the degree to which such activities might encroach upon their full-time responsibilities at NIH.

Furthermore, a committee was established at NIH to coordinate biotechnology activities. This NIH-wide group has been considering the policy suggestions made at the June meeting of the Advisory Committee to the Director, NIH. Its members have held discussions with representatives of the Industrial Biotechnology Association, the Association of Biotechnology Companies, and the American Society for Microbiology as well as with individuals interested in biotechnology. In addition, the NIH has sponsored a symposium attended by representatives of the Industrial Research Institute and has convened a small group of scientists to examine the Federal role in the area of research and research training in biochemical engineering.

Another interagency committee, the Biotechnology Science Coordinating Committee (BSCC), was established on October 31, 1985, as part of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET). The BSCC will have the responsibility to review the regulatory decisions of the various agencies related to the use of recombinant DNA techniques in procedures for which there is concern regarding release of

engineered organisms. The chair of the new interagency committee will be shared on a rotating basis by the NSF Assistant Director for Biological Sciences and the NIH Director. Thus, the NIH will play a central role in the new plan for Federal coordination of biotechnology.

While the NIH does not "regulate" per se, it has received recognition for the responsible manner in which its Recombinant DNA Advisory Committee (RAC) has managed the introduction of a host of new uses for biological manipulation. Recently, for instance, the RAC has developed and disseminated a set of "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols" to guide research in this important emerging area of science.

The NIH is providing substantial research training support in the areas of cellular and molecular biology, genetics, and molecular pharmacology in order to meet future needs for biotechnology research personnel. The training needs are less clear in the area of bioprocess engineering. A recent study indicates, for example, that while biotechnology firms have projected a severe shortage of personnel, the actual growth of their staff has proceeded at a pace slower than expected. The NIH contributes support to the training component of the MIT Bioprocess Engineering Center, a National Science Foundation initiative in biotechnology.

Discussion of additional means to assist the growth of the Nation's biotechnology industry will continue. The NIH investment will be designed to ensure the stable and continuing growth in the knowledge base on which more focused research and development must build.

#### **Care and Use of Animals in Research**

The National Institutes of Health has long recognized both a scientific and an ethical responsibility for the humane care and treatment of animals used in biomedical research. At the June 1984 meeting of the Advisory Committee to the Director, NIH, representatives from both the biomedical research community and



*Different strains of mice are studied to identify unique genetic characteristics.*

the animal rights movement discussed many aspects of the animal welfare issue, including Federal policies, legislation, and the responsibilities of institutions and investigators. The deliberations helped to forge a broadened effort at NIH to examine the adequacy and effectiveness of existing policies, to strengthen implementation of those policies, and to improve conditions in extramural and intramural laboratory animal facilities.

#### *Extramural Program Initiatives*

The NIH played a major role in revising the PHS policy and the NIH guide governing animal welfare programs at awardee institutions. The "PHS Policy on Humane Care and Use of Laboratory Animals by Awardee Institutions" implements the principles for the use of animal experimentation developed by the Interagency Research Animal Committee. The revised PHS policy strengthens the assurance system and provides for establishment of Institutional Animal Care and Use Committees, with increased responsibility and authority.

The "Guide for the Care and Use of Laboratory Animals" is the basis for animal care programs funded by PHS agencies, including the NIH. Revision of the Guide was supported by NIH contract and prepared by the Institute of Laboratory Animal Resources of the National

Research Council. Revisions of both the PHS policy and the Guide reflect broad public comment.

Failure to comply with requirements of the policies can lead to suspension or termination of an award, or to ineligibility for future funding. The NIH investigates all allegations of noncompliance. The NIH Office for Protection from Research Risks (OPRR) conducts announced and unannounced site visits to assess the adequacy of animal welfare assurance systems at awardee institutions and continues to sponsor a series of regional workshops open to institutional administrators and others who share in responsibility for sound management of humane animal research.

#### *Intramural Program Initiatives*

The same policies on humane care and use governing extramural animal research apply to the intramural programs. Compliance with these policies by all intramural Institutes and Divisions is ensured by the Deputy Director for Intramural Research. The responsibility is carried out within a framework of BID Animal Research Committees advisory to Scientific Directors and a central NIH Animal Research Committee advisory to the NIH Deputy Director for Intramural Research.

Although the NIH houses the

majority of its animals in central holding facilities that are AAALAC-accredited, many animals are housed in decentralized facilities scattered in various laboratory buildings. In 1983, each BID Animal Research Committee was given the responsibility to develop a plan for obtaining accreditation of the animal facilities and management practices or for pursuing accreditation standards.

Following a special meeting of the BID Directors on August 13, 1985, the NIH initiated an accelerated program with the goal of meeting AAALAC requirements for all intramural facilities no later than the end of FY 1987, and achieving accreditation as soon as possible thereafter. Under direction of the Oversight Committee on AAALAC Accreditation, a number of task forces, composed of veterinarians, scientists, and facilities staff, developed a plan to meet this goal for the intramural facilities, with all renovation and construction projects to be under way by October 1987.

### Other Initiatives

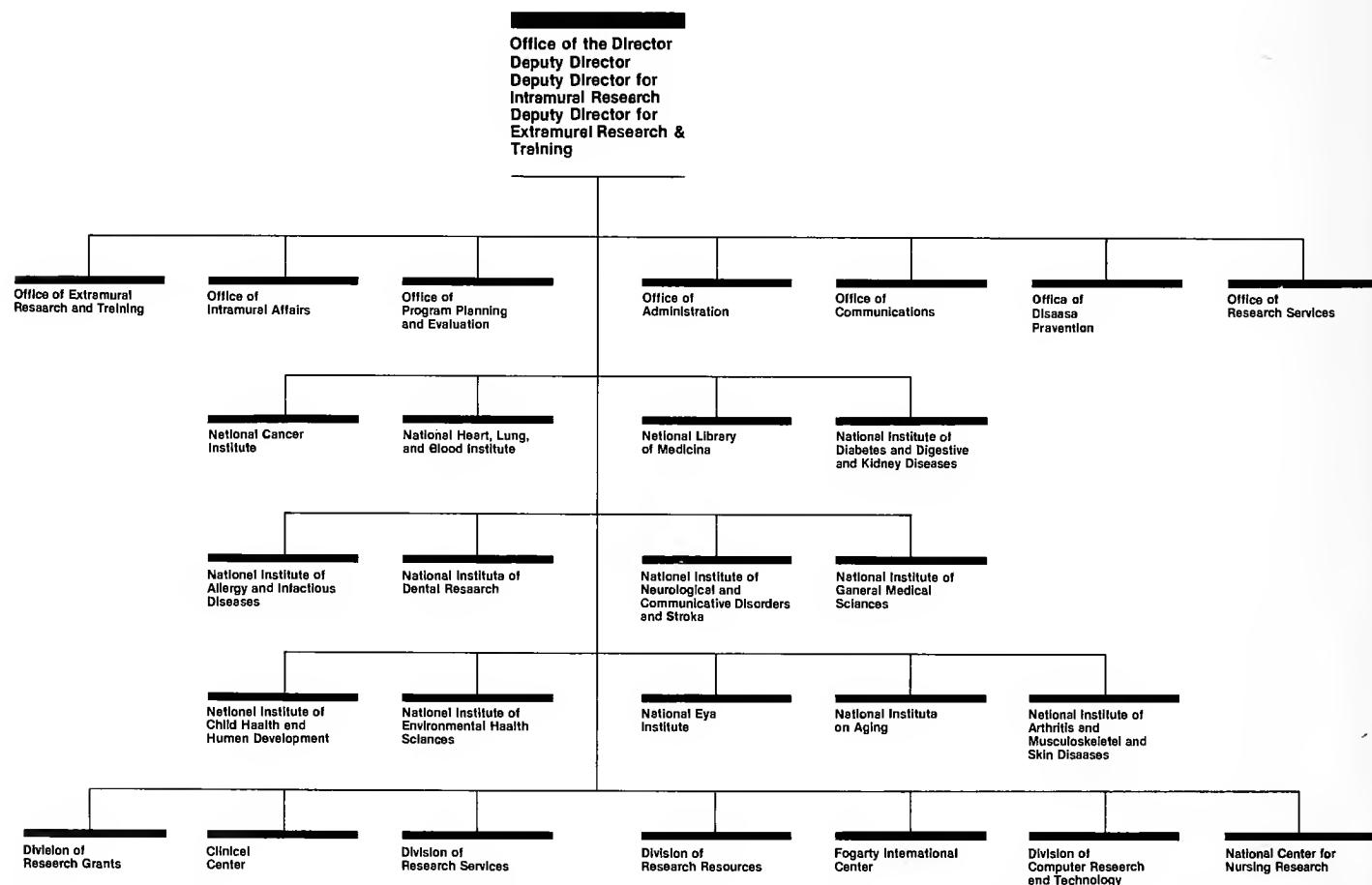
Recent interest in the use of model systems in a wide range of biomedical research has prompted the Division of Research Resources to establish a program to develop various lower-animal, *in vitro*, mathematical, and computer models for research. The DRR will be assisted in these efforts by findings of the National Academy of Sciences (NAS) study, "Models for Biomedical Research: A New Perspective," funded by the NIH. Another study for which the NIH has provided partial funding is the NAS multi-phase study, "Uses of Animals in Research." The first phase will cover the extent of the use of animals in research and the second will address some of the broader issues in this area.

### Animal Welfare Legislation

Over the past 10 years, public and congressional concerns have led to introduction in the Congress of numerous measures related to research animals. In general, concerns have centered on whether

excessive numbers of animals are used in research and whether Federal funding agencies provide adequate oversight of research that involves the use of animals.

The Federal Animal Welfare Act, passed on December 23, 1985, is the most recent legislation relevant to the care and use of research animals. The law requires the Secretary of Agriculture to promulgate standards applicable to animal research facilities regulated under the Animal Welfare Act and to consult with the Secretary of the Department of Health and Human Services prior to the issuance of regulations. A subcommittee of the Trans-NIH Coordinating Committee on Research Animal Resources has been reviewing proposed USDA regulations. In addition, the Health Research Extension Act of 1985 contains a provision for NIH Animal Care Committees to assure compliance with the Guide. A framework to accomplish this is now in place.





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# **Section 2**

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## **Improvements in Grant and Contract Accountability and Technical and Scientific Peer Review Procedures**

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# Improvements in Grant and Contract Accountability and Technical and Scientific Peer Review Procedures

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## Introduction

Soon after the end of World War II, developments began to unfold that set the pattern for the support of biomedical research in this country. Prominent among these early developments was the decision by the NIH to augment and enhance the research carried out in its fledgling intramural laboratories at Bethesda by creating a program of broad research grant support to university-based scientists for the conduct of free-ranging individual basic and clinical investigations across the full spectrum of the biomedical sciences. At the outset, the decision was made that the allocation of funds would be based on a national competition to select for support the best research ideas and proposals as judged by panels of scientists selected from across the Nation on the basis of their demonstrated expertise in the various relevant areas of science. It was decided also that the panels of expert scientists would be buttressed by national advisory councils or boards to review the program relevance of grants and to advise the categorical Institutes on broad policy matters and issues of general program direction. Thus were established the basic tenets, policies, and structures which have led directly to the present-day peer review system and the array of support instruments and extramural procedures through which biomedical research is funded.

The NIH makes approximately 20,000 extramural awards to more than 1,200 institutions in every state of the Union and to a number of foreign countries. The NIH relies on three major funding mechanisms as the administrative instruments for

accomplishing its program goals through the efforts of scientists outside the NIH.

The mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts).

## Financial Assistance Awards

### Grants

Grants for health-related research and research training projects or activities make up the largest category of funding provided by the NIH. These grants encourage and support meritorious projects or programs in all scientific fields related to health and span the spectrum from basic and applied research in laboratory and clinical settings to evaluation, demonstration, and dissemination of new medical technologies. In addition, grants are awarded to create and sustain certain special resources or facilities for such research.

Grants are used when the idea for the research or training project is initiated by the investigator; when there is no substantial program involvement anticipated between the funding Institute or Division and the recipient during performance of the activity; and there is no expectation on the part of the funding Institute or Division for delivery of a specified product or service. A grant may provide funds for essentially all reasonable costs of the activity. Grant applications may request, in most instances, an approximate amount of financial support and the duration of time, usually no more than 5 years, needed to complete the project. Funding is accomplished in annual increments. Research grants include research project grants, program project grants, FIRST and

MERIT awards, center grants, resource grants, and conference grants.

### Cooperative Agreements

Cooperative agreements are similar to grants in that they are awarded by NIH to assist and support research and related activities. They differ, however, in that grants require minimal or no involvement of the awarding Institute or Division during the performance of project activities, but cooperative agreements give a substantial programmatic, i.e., scientific and technical, role to the Institute or Division. This role may involve cooperation or coordination to assist awardees in carrying out the project or, in some cases, review and approval of certain processes and phases in the scientific management of the project.

Policies and procedures for application, review, and administration of cooperative agreements are similar to those for grants. An important difference, however, is that the Institute or Division must issue a specific program announcement or RFA describing the program, functions or activities that it proposes to support by cooperative agreement and the nature of the proposed Institute or Division staff involvement. Terms and conditions, above and beyond those required for the normal stewardship of grants, must be negotiated to establish the rights, responsibilities, and duties of the prospective awardee and the Institute or Division, based on the terms and conditions outlined in the program announcement.

### Review Process

Applications are subjected to a peer review process that is based on two



sequential levels of review, both of which are required by law. The first level of review is performed by initial review groups composed of at least 75 percent non-Federal scientists selected for their competence in particular scientific areas. An NIH health scientist administrator serves as executive secretary of the review group. The task of the IRGs is to evaluate the application for scientific and technical merit.

In considering the scientific merit of each application, the members of the IRG assess:

- scientific, technical, or medical significance and originality of the proposed research;
- appropriateness and adequacy of the experimental approach and methods to be used;
- qualifications and experience of the principal investigator and staff in the area of the proposed research;
- reasonable availability of resources necessary to the proposed research;
- reasonableness of the proposed budget and duration in relation to the proposed research; and
- where an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against such effects.

For each application a recommendation of approval, disapproval, or deferral for additional information is made by majority vote. In addition, for each application recommended for approval, each member of the IRG individually and privately records a numerical score that reflects a personal evaluation of the relative scientific merit of the proposed research or training. The numerical score is based on a scale ranging from 1.0 (the best) to 5.0 (the least acceptable) score. After the meeting, the executive secretary averages the individual reviewers' scores for each approved application and multiplies by 100 to provide a three-digit rating known as a priority score. Priority scores assist the staff of the Institute or Division in determining which applications are to be funded.

The second level of application review is made by the national advisory council or board associated with the awarding Institute or Division. These groups are composed of both scientific and lay representatives who are chosen for their expertise, interest, or activity in matters related to the individual Institute or Division missions. Council or board recommendations are based on judgments about both scientific merit and relevance to Institute or Division program goals. In general, the NIH may make an award only if the application has been recommended for approval by a national advisory council or board. They may also become quite involved in an Institute's or Division's overall program and its research planning process, which would include the allocation of resources for both grants and contracts.

### **Acquisition Awards**

#### *Contracts*

NIH awards research and development (R&D) contracts to nonprofit and commercial organizations for scientific inquiry directed towards particular areas of research and development to utilize advances in knowledge and technology in searching for solutions to specific questions. Contract performance is closely monitored by NIH to help ensure accomplishment of project goals for the benefit of or use by the awarding Institute or Division.

Most NIH research and development contracts are the cost-reimbursement type, i.e., the NIH pays the contractor all allowable, allocable, and reasonable costs in performing the project. In addition, fees may be paid in some cases. The types of contracts awarded by the NIH include research contracts, development contracts, demonstration contracts, research and development support contracts, and scientific communication and evaluation contracts.

The review process for R&D contracts differs from that for grants in that all offerors respond to a Government-defined statement of work contained in a solicitation document

called a Request for Proposals (RFP), and the proposals submitted are reviewed against fixed evaluation criteria that are specified in the RFP. Consistent with statutory and regulatory requirements for peer review of NIH-solicited contract projects, which comprise the larger share of NIH R&D contracts, the concept of each is evaluated by a scientific review group composed of at least 75 percent non-Federal advisors who provide advice regarding the merits of the basic purpose, scope, and objectives of the proposed project. Advisory conferences and workshops also serve as sources of valuable ideas and guidance.

Institute or Division program and contracting staff translate the advisory group review results and recommendations for contract projects into RFPs. These describe in some detail the specific project requirements and the criteria by which the proposals will be evaluated. After further reviews within the Institute or Division and, in the case of large awards, by the Office of the NIH Director, the Institute or Division then issues the solicitation.

Solicited contract proposals undergo review by advisory peer evaluation groups whenever the RFPs seek offerors to provide innovative and original approaches to accomplish the tasks described in the RFP. When the RFP defines both the project requirements and approaches and asks offerors only to describe the capabilities of their staff and facilities to undertake the proposed project, the proposal evaluations may be conducted by Government employee review groups which may also include external reviewers. All proposals are evaluated strictly in accordance with criteria specified in the RFP.

Evaluations and recommendations of the evaluators, taken jointly with the results of separate NIH staff evaluations of the cost proposals by NIH staff, provide the bases for discussions with offerors in the competitive range, offerors' submission of revised proposals and subsequent review and selection of the awardee by the contracting officer

(with the advice of Institute or Division senior staff) and for final negotiations with the selected contractor.

Institutes or Divisions occasionally make awards in response to unsolicited contract proposals when these meet specific Institute or Division program needs and when there is adequate justification for a noncompetitive award. In these instances, peer reviewers routinely evaluate both the concept and the approach for the proposed project. Subsequent evaluations and negotiations are similar to those for solicited proposals. In contrast to the statutory requirement that grants be recommended for approval before being funded, the advisory councils and boards are not required to certify their approval of individual contract projects.

Each year the NIH undertakes initiatives designed to improve policy and procedures governing the administration of extramural activities and the peer review process. Highlighted here are some of the initiatives undertaken in FY 1985.

## **Grant and Contract Accountability**

### **Florida Demonstration Agreement**

Under the auspices of the Government-University-Industry Research Roundtable, sponsored by the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, the NIH and four other Federal agencies have initiated a demonstration project with the Florida State University System and the University of Miami. The other Federal agencies participating in the project are the National Science Foundation, the Office of Naval Research, the Department of Energy, and the Department of Agriculture. The purpose of the project is to standardize and streamline administrative procedures in the post-award phase for research grants.

The core of the Demonstration Project is the use of a standard instrument by the agencies providing research support to the univer-

sity system. The agencies will use a standard set of general terms and conditions for the post-award administration of research grants and will supplement this standard set of terms with agency-specific provisions only to the extent necessary to meet legislative and administrative requirements.

The central features of the general terms and conditions are:

- elimination of Federal requirements for prior approvals, except for change in the scope of the research effort, change of the investigator, and change of the awardee institution;

- simplification of administrative procedures, such as the authorization to universities to allow 90 days' preaward costs, a one-time, 12-month, no-cost extension, carryover of unobligated balances with no Federal prior approvals, and the requirement only for annual progress and financial reports;

- introduction of the option, with approval of the funding agency, or agencies, for the administrative and accounting unit to be the investigator's total research program, rather than individual project's; and

- assurance of accountability in research and in administrative procedures, with fewer transaction-by-transaction reviews during performance, including preaward approval of the recipient's pertinent business and management systems, review of research progress, and audit review.

The Demonstration Project began in March 1986, and will run for a period of 2 years. Implementation at NIH started in May, with investigator-initiated research project grants (RO1's) awarded October 1, 1985, and beyond. As new RO1s are awarded, they will be incorporated into the agreement and designated as such on the Notice of Grant Award.

### **Research and Development (R&D) Contracting Function**

In FY 1985, the NIH continued with efforts to implement the provisions of the Competition in Contracting Act of 1984 (CICA), in order to increase the effectiveness and equity of NIH R&D acquisitions. With the CICA and other legal and regulatory policy issuances that

emphasize the need to fulfill Government acquisitions by competitive contracting, the NIH succeeded in awarding 81 percent of its actions (almost 86 percent of dollars obligated) competitively. Among other significant accomplishments towards effectiveness and equity in contracting are the following:

- issuance of major revisions in R&D contracting policies and procedures, and arrangement of training for NIH contracting and program staff to comply with CICA provisions;

- completion of a followup procurement management review of National Cancer Institute contracting operations as requested by Senator Orrin Hatch's staff and the Office of the Inspector General, DHHS;

- accomplishment prior to award, of 108 Board of Contract Awards reviews of high-dollar R&D contracts to be sure that required clearances were obtained, technical reviews were fairly and adequately performed, the competitive range was established properly, and negotiations were conducted with all offerors in the competitive range;

- completion of 90 Presolicitation Board reviews of RFPs prior to their release to ensure the adequacy of plans for peer reviews of project concepts and proposals, clear and adequate statements of work, appropriate technical evaluation criteria, possible socioeconomic set-asides, and overall potential for the RFP to engender meaningful competition;

- review of 83 justifications for other than full and open competition to ascertain that requests for that action clearly stated the requirements and justification for exclusion from the competitive marketplace; and

- arrangement of general acquisition courses for 201 NIH contracting staff, CICA training for an additional 156, and project officer training for 223 NIH scientists and health scientist administrators.

These and related efforts continue in FY 1986 to help ensure equity, accountability, and effectiveness in NIH R&D contracting activities.

## Misconduct in Science

Public funding of biomedical research has traditionally required accountability in terms of appropriate expenditure of funds and fulfillment of the purpose of the award. In recent years, the NIH has been faced with new issues of accountability, requiring the agency to deal with instances of fabrication of data, misrepresentation of findings, and failure to provide adequate protection for human and animal subjects of research. While documented instances of misconduct are rare, it has become clear that formal procedures are necessary to evaluate and investigate possible misconduct and take appropriate action when misconduct occurs.

In FY 1985 and early 1986, the NIH, acting as the lead agency for the Public Health Service (PHS), has coordinated the development of policies and procedures for dealing with possible misconduct in research that is funded, conducted, or regulated by the PHS. The procedures, approved by the Acting Assistant Secretary for Health in April 1986, are based in large part on NIH experience in investigating several instances of actual or apparent misconduct during the past 5 years and provide guidance for agency staff.

The procedures specify the responsibilities of organizations that accept PHS funds. In brief, awardee institutions will be required to develop their own policies and procedures for dealing with possible misconduct and to inform the PHS of the initiation of a formal investigation. In complying with Section 493 of P.L. 99-158, the Health Research Extension Act of 1985, the NIH has developed a notice of proposed rulemaking on behalf of PHS, to be published during the summer of 1986. The proposed regulation will require each applicant organization to submit an assurance that it has policies and procedures for dealing with possible misconduct, and that it will inform the Secretary of any formal investigation of misconduct.

During this period NIH also investigated several cases of alleged misconduct and provided advice to other agencies and awardees regarding the development of procedures and the resolution of individual instances of misconduct.

## Revision of Grant Application Form

The Public Health Service research grant application form (PHS 398) is used by nonprofit, profit, and government organizations to apply and compete for grant funds appropriated to the various awarding components of the Public Health Service. At regular intervals the use of this application form and its associated forms and instructions must be approved by the Office of Management and Budget. When the application forms are submitted to the OMB for clearance, they are reviewed by NIH and PHS staff to determine if any changes are required. This past year's review led to a decision to make major modifications in the application form. These changes were made to provide an application that would significantly reduce the burden of preparation on applicant investigators and organizations.

The principal modifications will now:

- expand the use of the PHS 398 to accommodate applications for Institutional National Research Service Awards, replacing application forms PHS 6025-1 and PHS 6025-2;
- include special instructions to use the PHS 398 to apply for a Research Career Development Award, replacing a separately published booklet of instructions; and
- place a 20-page limitation on the narrative section of the application, in which the investigator describes the project for which support is being requested.

Other significant modifications include:

- adding a block on the first page of the application form to indicate whether or not vertebrate animals are to be used in the project;
- adding consultants and collaborators to key professional personnel on page 2 of the application form, to help identify and thus

avoid potential conflicts of interest in the review process;

- redesigning the budget page to obtain more useful information regarding time and effort of all personnel participating in the project; and

- adding to the checklist a block to indicate approval of an assurance related to scientific fraud, as required by P.L. 99-158, the Health Research Extension Act of 1985.

In the instructions, sections were added on scientific fraud and the NIH review appeals system, and the section on the use of vertebrate animals was revised to provide more detailed information for use by PHS staff and peer review groups. The application form will also be redesigned for future electronic scanning and submission of applications by applicant organizations. These revisions should improve accountability and improve the efficiency and productivity of NIH peer review processes.

## Additional Improvements

Other improvements in the operation of the extramural awards system included:

- *New Research Grant Awards.* The NIH has initiated two new major research grant awards to enhance the stability and productivity of principal investigators. Known as the FIRST and MERIT awards, they represent the culmination of a great deal of NIH staff effort and interaction with the extramural community; they are described in some detail in Section I of this report under NIH-Wide Policy Issues.

- *Selection of Award Instrument.* During FY 1985, efforts to refine the NIH-wide guidelines for the proper selection of extramural award instruments (grants, cooperative agreements, and contracts) were completed. These guidelines were developed with significant input from the PHS Office of Grants and Contracts, were derived from earlier OMB, HHS, and PHS documents, and provide substantial explanations and examples to guide NIH program staff in selecting the proper award instrument.

- *Review of Cooperative.*

**Agreements.** The NIH has also developed instructions for the central review of Institute and Division plans to use cooperative agreements (CAs). Each Institute program office must prepare and submit to the Office of Extramural Research and Training (OERT) a memorandum justifying the planned use of a CA, and an accompanying draft Request for Applications (RFA) announcing details of the plans for the CA activity for publication in the NIH Guide for Grants and Contracts. A Cooperative Agreement Panel reviews these documents and recommends action on the plan to the Associate Director for Extramural Affairs (ADEA). The ADEA decides on the merits of the planned use for the CA and advises the Institute accordingly.

## Peer Review Procedures

### Peer Review Appeals System

Significant progress was made during FY 1985 in developing and implementing a grants peer review appeals process. Guidance was developed concerning the handling of communications and appeals; was discussed with and agreed upon by the NIH Institutes and their National Advisory Councils or Boards and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); was publicized broadly at NIH, to the members of all NIH initial grant review groups and other groups, including the senior ADAMHA staff; and was announced in several internal and external NIH publications.

In early FY 1986 the appeals process became operational throughout NIH. Under the process, applicants may request an examination of their concerns relating to the referral and peer review of their applications. Such concerns may involve situations such as:

- the NIH refusal to accept an application;
- a dispute about the assignment of an application to an initial review group or to an NIH Institute or Division;

- a perceived insufficient expertise on the initial review group or site visit team, or conflict of interest on the part of review group or team members;

- apparent factual or scientific errors, oversights, or bias associated with the review of an application at the initial or advisory council review; and

- possible inappropriate handling of the application or the review.

Under this process, the principal investigator first directs any concerns to the Institute or Division which is responsible for the application, and, if shortcomings are found to have occurred, their staff makes every effort to rectify them in a timely manner. If the principal investigator seriously disagrees with the resolution of his or her concerns by the Institute or Division, the investigator and applicant organization may jointly appeal to the Office of Extramural Research and Training, in the Office of the Director, NIH. There the appeal is examined independently, frequently in consultation with scientific or other experts, and the final NIH decision on the appeal is rendered by senior NIH officials responsible for extramural research (i.e., the NIH Deputy Director for Extramural Research and Training, the Director of the Division of Research Grants, and the Director of the Institute or Division in charge of the application).

The appeals process is NIH's response to numerous requests from the scientific community for a well-defined and uniform approach for dealing with review-related concerns. It amalgamates NIH's responsibilities to applicants, as required by law, with its established practices for discharging such responsibilities in a responsive and equitable manner.

### Additional Policy Developments in Peer Review

A wide range of additional policy initiatives was undertaken in FY 1985 to improve peer review procedures. These included:

- the presentation of a 2-day module or course on issues in peer review, involving NIH staff and speakers from the academic community discussing new developments in the grant review process;

- the issuance of a chapter in the NIH Manual on review of program project applications, culminating nearly 2 years' effort;

- the issuance of an Instruction and Information memorandum clarifying grant application review procedures for confidentiality of review materials and for recording and calculating priority scores for split votes;

- the revision of internal guidelines for reviewing individual National Research Service Award (NRSA) applications to standardize review criteria for all involved study sections and to expedite review of applications;

- the initiation of an effort to develop revised or refined guidelines for preparing initial review group summary statements;

- the initial consideration of requirements for guidelines for the review of cooperative agreement applications, with particular attention to procedures for competing continuation applications; and

- the consideration of procedures for the use of *ad hoc* special review group consultants in evaluating applications and proposals.

All these efforts are designed to achieve greater understanding and more standardized implementation of peer review procedures, thereby enhancing the quality and effectiveness of the review process.

## Peer Review of Intramural Research

The intramural research program of the NIH are also subjected to scientific review. Over the past 30 years these programs have been reviewed and evaluated by groups of outside scientists, and the NIH continues to seek ways to strengthen this process. NIH policy states that "all research conducted intramurally must be reviewed regularly by highly qualified outside scientists." Each research Institute has a Board of Scientific

Counselors, as the intramural peer review groups are called, which meets two or three times each year to review in detail the work of one or more laboratories, and all the career scientists in those units. Each laboratory in the NIH intramural program is reviewed at least once in 4 years. The purpose of the review are to:

- examine the research that has been done since the last review and appraise its quality and relevance to the Institute's mission;
- look at research planned for the immediate future and advise on its importance and feasibility;
- review the research of individual scientists and judge their progress;
- advise, when appropriate, on the allocation of positions and funds to particular research areas;
- review the work of younger scientists being considered for tenured positions and make recommendations; and
- provide strategic advice and counsel to the Scientific Director on program structure and future directions.

The typical review process, in brief, includes the following steps:

- Boards are established and Board members appointed (except in the National Cancer Institute) by the Director, NIH. A primary consideration of scientific qualification for Board membership is international recognition as an authority in the fields under review. Boards usually number six to eight members (those in NCI, with some grant and contract review responsibilities, are larger).
- The Institute's laboratories and branches are scheduled for review in sequence so that all will be evaluated within the 4-year span of the Counselors' appointments.
- A brief written description of the research to be reviewed is prepared in advance, and sent to each member of the Board of Scientific Counselors along with curricula vitae and bibliographies of all the scientists, lists of all the staff, summaries of lab budgets and space, and any research support

contracts. The individual Institute Scientific Director usually, also, invites one or more ad hoc experts as needed to supplement the expertise of the regular Board members.

- At the meeting, which usually lasts two or two-and-a-half days, a variety of formats may be used. Usually all the tenured scientists and some of the junior staff report orally on their present and planned research and are questioned. In some instances systematic individual or group interviews are used. Opportunity is usually provided for Counselors to visit laboratories and talk informally with staff members.

- The Chairman and other Counselors prepare a written report of their findings and recommendations, which is submitted within 4 months to the Scientific Director for information and transmittal to the Director of the Institute, the NIH Deputy Director for Intramural Research, and the Director, NIH.

- The Board's report is scheduled for review by the Board of Scientific Directors of all the Institutes, and its findings and recommendations, along with the description of the research reviewed, is transmitted to the Institute's National Advisory Council for its information and possible comments.

- At an early subsequent meeting of the Board of Scientific Counselors, the Scientific Director reports back on the actions taken on their previous recommendations.

The procedures for peer review were codified and published as a chapter in the NIH Manual in March 1985, under the title "Review and Evaluation of Intramural Research." After the passage of the Health Research Extension Act of 1985, the Manual Chapter was revised to include the requirement from that law that reports by Boards of Scientific Counselors be submitted to the appropriate National Advisory Council for their review and possible comment. The revised Manual Chapter was issued August 4, 1986.

As a result of the issuance of the original and revised Manual Chapters, peer review procedures were clarified and tightened in several ways during the past year. They include:

- The specific requirement that all intramural research, including that carried out on a part-time basis by staff of some non-research Divisions, shall be reviewed by Boards of Scientific Counselors.
- The requirement that written reports by Boards shall be completed within 4 months of the meeting date.
- The requirement that Scientific Directors report back to their Boards at the earliest practicable meeting date the actions taken with regard to the recommendations of the Board.
- The requirement, as contained in Public Law 99-158, that the results of the review, along with the written description of the research reviewed, be submitted to the appropriate National Advisory Council for its review and possible comment.



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# **Section**

## **3**

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**NIH Research  
in Disease  
Prevention**

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### Introduction

Research into the prevention of disease has increased in complexity due to a shift in the relative prevalence of such chronic diseases as cancer and diabetes as compared to infectious diseases such as pneumonia and tuberculosis—the latter were more common at the beginning of the century. In the past, prevention research has focused primarily on serious infectious diseases caused primarily by bacteria and viruses. Now it must cover a multitude of other types of diseases with many diverse causes, methods of occurrence, and disease mechanisms, many of which are as yet unknown. The prevention of disease has become a particular challenge to the research scientist as rapidly rising health care costs and chronic conditions make prevention paramount to cure.

The National Institutes of Health has long been involved in prevention-related research, although such activities have not always been so identified. The main goal of the NIH is to acquire new biomedical knowledge that ultimately can be used to prevent disease, since prevention clearly is the most useful extension of knowledge in the health field. At the NIH, research in prevention has as its objective both the protection of individuals from disease and the prevention of the progression of disease to disability or death.

Research occurs along a spectrum from the quest for new scientific knowledge to the dissemination of proven findings. To describe the spectrum of NIH activities in prevention, we have divided research efforts into the following four categories: basic research, applied research and clinical investigation,

intervention studies, and professional and public education. This sequence demonstrates the continuum of basic and clinical research efforts aimed at developing preventive interventions that ultimately will be translated into health care practice as soon as they can be demonstrated to be safe, effective, and feasible. Although the following program descriptions illustrate highlights of NIH research in prevention, they are by no means meant to be an exhaustive accounting of total NIH prevention efforts.

The acquisition of new biomedical knowledge is a serendipitous process. One does not know where or how new knowledge gained will be applied to specific human diseases. For example, research supported by the National Institute of Allergy and Infectious Diseases over the past 20 years has helped toward understanding the cancer problem, whereas research recently supported by the National Cancer Institute is now having relevance to infectious diseases, for example AIDS. For this reason it is difficult, and perhaps inappropriate, to place biomedical research into discrete entities, and therefore, the categorizations that follow are not meant to be absolute but to serve as a demonstration of the depth and breadth of NIH prevention research endeavors.

### Basic Research

Basic research encompasses the quest for new knowledge, the answers to basic questions, for example: What are the causes or underlying mechanisms of a given disease or disease systems? Are there other contributing factors? How do these interact with normal

biological processes? Can the interaction be interrupted, reversed, or prevented in order to prevent or halt the progress of the disease?

One of the most thoroughly studied disease-causing agents is tobacco or, more specifically, the effects of cigarette smoking on health. Additional basic prevention studies investigate the role of other environmental substances in the causation of disease and seek measures that can be taken to prevent these diseases.

### Smoking and Health

Epidemiologic studies investigate factors determining disease frequency and distribution among populations. Epidemiologic studies of the health effects of tobacco use have recently focused on two relatively new areas of interest: lung cancer risk associated with passive smoking (involuntary inhalation of the smoke from others' cigarettes) and oral cancer development as a consequence of the use of smokeless tobacco. NIH investigators have participated in two recent studies that have strengthened the evidence for the association of passive smoking with lung cancer risk. Each experiment was a case control study—one in Japan and the other in the United States. Both studies revealed that the risk of lung cancer for the wife tended to increase with the amount smoked by the husband, with the excess reaching twofold or higher among nonsmoking women whose husbands were heavy smokers.

In neither study could confounding variables account for the association with passive smoking. The results of these two investigations are consistent with other reports and support the hypothesis of a possible association between passive



smoking exposures and lung cancer. While the total evidence is not definitive, the results are suggestive enough to warrant further evaluation in larger studies where passive smoking exposures can be more fully quantified.

The use of smokeless tobacco has been linked to high rates of oral cancer, particularly among women in the southern United States. Efforts now are being focused on clarifying the cancer risks associated with snuff dipping and chewing tobacco, particularly because the use of such materials appears to be on the increase among young people in the United States. The recent NIH Consensus Conference on the Health Effects of Smokeless Tobacco and the Surgeon General's Report entitled "The Health Consequences of Using Smokeless Tobacco" are intended to make more widely known the dangers associated with the use of smokeless tobacco and thereby to stimulate an important public health cancer prevention initiative.

**Biochemical Indicators of Disease**  
NIH scientists are using state-of-the-art mechanistic information such as dioxin receptor interactions, DNA adduct (interaction of a chemical or its metabolites with DNA) quantitation, and oncogene\* evaluation that may lead to removal of some of the highly uncertain assumptions made in species extrapolation of risk, including carcinogenesis. Studies of DNA adducts or the products of interaction of a chemical or its metabolites with DNA in human placental tissue have provided the first clear demonstration in humans of DNA adducts associated with cigarette smoking. The major adducts being formed by cigarette smoking *in vivo* do not seem to be caused by the polycyclic aromatic hydrocarbons or amines usually thought to be the most dangerous components of cigarette smoke. This work may lead ultimately to the identification of specific cigarette smoke components as well as other environmental exposures that damage human DNA.

\* *Tiny pieces of DNA that may be part of the normal genetic makeup of human cells and that, when altered by environmental agents, may initiate the cancerous process.*

In their work on oncogenes, NIH scientists have characterized the properties of activated oncogenes in spontaneous tumors and in some chemically induced tumors in mice and rats. Results show that oncogene activation in spontaneous tumors is different, in some cases, from that observed in chemically induced tumors. This finding provides an approach to increase the sensitivity of chronic animal tests for detecting carcinogens. This, in turn, may permit identification of those cancers caused by chemicals and even some of the chemicals involved.

### **Mechanisms of Action of Hazardous Substances**

Basic research in environmental health sciences is at a major turning point in its evolution. While work must continue to determine which naturally occurring and man-made substances are hazardous to human health and which are not, major advances in the understanding of the ways in which hazardous substances cause illness are being achieved. This increase in knowledge of the basic mechanisms of disease, coupled with improved environmental testing to determine patterns of pollution and with epidemiologic study, should lead to interventions designed to prevent environmentally related illnesses and premature deaths.

### **Detoxification, Inactivation, and Transformation of Carcinogenic and Other Agents**

An area of NIH basic prevention research focuses on the study of a group of enzymes known as the "mixed function oxidase system." The cytochrome P450's are a major component of this system and are important because, as receptors for foreign chemicals, they are responsible for detoxifying or inactivating a wide variety of drugs, carcinogens, and other environmental agents. They also have the ability to transform some types of chemicals (procarcinogens) into active carcinogens. Whether or not a chemical is carcinogenic is determined, to some extent, by the balance between detoxification and activation. For a

given chemical, this balance can vary according to species, sex, hormone status, previous chemical exposures, and a number of other factors. Monoclonal antibodies to various forms of cytochromes P450 have been prepared; soon they will be applied to the identification of individuals and populations at increased risk of cancer either because they have a below-normal ability to detoxify chemicals or an enhanced ability to activate procarcinogens, thus providing an important opportunity for applied preventive measures.

### **Effects of Dietary Constituents on Carcinogens**

Another group of NIH investigators is studying dietary constituents that may modify the actions of carcinogens. These researchers have demonstrated that a newly identified antioxidant, indol-3-carbinol, a natural dietary constituent, suppresses metabolism of carcinogenic chemicals and inactivates dangerous chemicals produced by such metabolism. Similarly, other researchers have isolated a compound from soybeans that has the ability to completely inhibit transformation of normal cells to cancer cells in culture at very low, nontoxic concentrations. This effect also has been observed in experimental animals where the appearance of intestinal cancer, brought on by a known chemical carcinogen, was completely inhibited by the addition of this extract of soybeans to the diet.

### **Prevention of Cancer in the Worksite**

The primary objective of worksite cancer research has been to reduce the incidence or mortality from cancer from all risk factors in populations that are at higher risk because of occupational exposures and in worksite populations with lifestyles that increase the risk of developing cancer.

Research initiatives include an interagency agreement between the NIH and the National Institute for Occupational Safety and Health (NIOSH) to conduct hazard evalua-

tion studies of current cadmium and chromium workers in order to identify feasible control measures and Phase III studies to reduce risk through secondary prevention (detection of disease in its early, treatable stage) among cohorts of workers at high risk for lung cancer due to asbestos exposure, bladder cancer due to aromatic amine exposure, and colorectal cancer due to nonspecific exposures in the tool and dye trades. Additionally, five union-approved education programs to identify and reduce exposure to workplace risks are being supported for the rubber, auto, steel, chemical, and painting industries.

### **Estrogenic Activity of Environmental Chemicals**

The mechanisms whereby various naturally occurring and synthetic chemicals show significant estrogenic activity in the human body and in laboratory animals is the research focus of one NIH laboratory. This goal is targeted because understanding the chemical-structural basis of estrogenic activity may help identify those occupational and environmental chemicals that have the potential for causing changes in the human reproductive system. An example of such a chemical is chlordecone (Kepone) which has been found to cause impotence and sterility in male workers. Estrogenic contaminants also are suspected of being associated with premature sexual development in very young children in Puerto Rico. Research at NIH on the pharmacology and structural biology of environmental estrogens has been instrumental in defining the toxicological properties that must be followed in order to deal with this potential human health problem. Other studies of developmentally estrogenized laboratory animals and humans are providing new insights into basic mechanisms of sex differentiation, genital tract pathobiology, and hormonal carcinogenesis. This insight provides opportunities for developing new therapeutic strategies for cancer prevention in estrogen target tissues such as breast, cervix, and uterus.

It also may identify different approaches to environmental monitoring of these compounds.

The health hazards inherent in reproduction, pregnancy, birth, infancy, and childhood also are of concern to NIH-supported scientists who seek to prevent disorders and diseases related to these developmental stages through better understanding of the inherent disease mechanism.

### **Isolation and Characterization of Inhibin**

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are the principal pituitary substances known to have a stimulating effect on the gonads. In both women and men, FSH stimulates the sex glands to produce eggs and sperm. For many years, scientists suspected that both male and female sex glands made a substance that regulated the secretion of FSH, but their attempts to isolate and purify the substance were unsuccessful. It was not until the advent of modern gene-splicing techniques that NIH-supported scientists isolated and characterized a protein called inhibin that appears to block the secretion of FSH, a hormonal step necessary for the development of sperm and egg cells. Over the years, scientists have also tested several FSH-inhibiting substances as male contraceptives but have had little success because side effects have kept the contraceptives off the market. This newly isolated protein, however, specifically inhibits the basal secretion of FSH but does not inhibit the secretion of luteinizing hormone, a reproductive hormone that indirectly controls sex drive in men. Because inhibin appears to block fertility without disturbing the rest of the body's hormonal balance, it may lead to improved birth control pills for women and provide a basis for the first hormone-based male contraceptive. Improved contraception will alleviate the health problems (low birth weight, abortion, and neglect of infant medical care) that are often the sequelae of unintended pregnancies. The accomplishment of the isolation and the characterization of inhibin not

only provides knowledge of the molecular structure of a substance that scientists may be able to develop as a safe contraceptive, but it also will help them to learn more about how hormones in both sexes control reproduction.

### **Prevention and Management of Premature Labor**

One in every 13 babies in the United States is born too early, too small, or both. These babies often have difficulty with functions as vital as eating and breathing, and many suffer serious lung problems, brain damage, and other disorders. Newborn deaths and birth handicaps could be reduced substantially if premature labor could be safely and reliably prevented.

The hormones of pregnancy and the factors that trigger labor appear to be similar in women and rhesus monkeys. By studying pregnant monkeys, NIH-supported scientists at the Oregon Primate Research Center are increasing our understanding of the processes involved in normal labor. Once the events involved in initiation of labor are fully understood, doctors can predict which patients are at risk for premature labor and can take preventive steps, including the use of safe and effective drugs that inhibit premature labor. These scientists are testing nifedipine in the pregnant rhesus monkey — carefully monitoring oxygen levels, heart rates, and uterine contractions. Nifedipine is a calcium channel blocker, selected for testing because calcium appears to be involved in the regulation of uterine contractions. The continuing efforts of this group of investigators will lead to better means of labor management in women.

### **Using Steroids in the Prevention of Hyaline Membrane Disease**

Hyaline membrane disease afflicts 50,000 prematurely born infants each year. It begins within the first minutes or hours of birth and is caused by the inability of the tiny air sacs in the immature lungs to remain properly inflated. The condition causes increased difficulty in breathing and, in the most severe

cases, leads to respiratory failure and death. In the United States, 9,000 newborns die from hyaline membrane disease each year.

The course of lung development is nearly identical in humans and macaque monkeys. Taking advantage of this similarity, a multidisciplinary research group supported by the NIH at the Wisconsin Primate Research Center (WPRC) is working to improve methods to hasten lung development using dexamethasone before birth of a premature infant. Dexamethasone is a synthetic steroid that has been shown to speed lung maturation, but there is little information regarding the proper dose to give the mother in order to provide adequate amounts of steroid to the fetus. The WPRC group has undertaken a systematic approach to ascertain the most effective dosage of steroid and to determine the efficacy of administering multiple versus single doses. Preliminary results indicate that dexamethasone therapy favorably influences the fetal lung in a dose-related fashion and that the multiple dose regimen may be more consistent in hastening lung maturation. This research will lead to improved methods for the prevention of hyaline membrane disease and, thus, lower the incidence of this syndrome in premature infants.

Some infants recovering from hyaline membrane disease have a disordered sequence of healing in which the lungs are severely scarred and further disease ensues. A type of hyaline membrane disease similar to that in humans occurs in prematurely delivered pig-tailed monkeys, and scientists at the Washington Primate Research Center, under an NIH grant, are attempting to understand exactly what malfunctions occur in the healing process. Attention has centered on factors affecting lung recovery, including oxygen that might compound lung injury, the phagocytic cells of the immune system that move to the site of lung damage, lung enzyme activity, and collagen synthesis. Knowledge gained from these studies will enable doctors to reduce the risk of

scarring in the lungs of premature infants recovering from hyaline membrane disease.

### **Genetic and Environmental Influences on Behavioral Development**

Within the past few years, the NIH has supported research on the genetics of behavioral development in a rhesus monkey model. The specially bred monkey appears to have one of two heritable types of behavior, "uptight" or "laid back." These behaviors were distinguishable not only under stress but also were detectable within hours after birth and throughout life. For instance, when the uptight monkeys were under stress, they displayed learning and communication disorders, depression, addictive behavior, and autism. Adult monkeys of the uptight type, when stressed, tended to have higher heart rates and even abused their offspring. In contrast, the laid back animals handled stress very well. This model of human behavior has great research importance because the monkeys seemed to display the full repertoire of normal and abnormal human behavioral development. These studies enabled the NIH investigators to study the genetic and environmental interactions that determine behavioral development, including the study of gene expression and hormonal regulation. The investigators also studied whether the expression of these heritable behavior patterns can be altered through environmental maneuvers, such as having the uptight infant monkey reared by laid back mothers, as well as early pharmacologic intervention.

In terms of humans, this research has the potential for increasing understanding of childhood behavior and behavioral disorders and the methods by which these disorders may be prevented or treated. It may shed light on the question of whether individuals at high risk for anxiety disorders also have a tendency toward cardiovascular or other bodily abnormalities and may lead to a better understanding of

the factors contributing to adult behaviors such as depression, addictions, and the full range of psychopathology.

### **Prevention of Dwarfism and Extreme Short Stature**

Children with hypopituitary dwarfism do not produce enough growth hormone of their own in their pituitary gland and, to attain normal stature, must receive supplemental hormone by injection. NIH-supported research on hypopituitary dwarfism has prevented, and continues to prevent, dwarfism in many thousands of children with this inherited condition. Recent research has shown that treatment with human growth hormone can help children with normal-variant short stature (height below the third percentile with no apparent organic cause) to increase their growth rate. Synthetic human growth hormone recently has been produced for the first time, based on recombinant DNA techniques developed with NIH support. Clinical trials of this new material (which, for the first time, will make human growth hormone available in unlimited amounts) have confirmed that its effects and potency are identical to those of the natural hormone, both in children and in adults. These recent developments have opened the door to successful future prevention of dwarfism and extreme short stature in many individuals.

Other research seeks to increase our understanding of and ability to prevent diseases often associated with the processes of aging.

### **Prevention of Cataract**

In an effort to understand how nutrition may be related to the serious problem of senile cataract—the opacification of the lens which occurs with aging—studies have been conducted on the development of cataracts in animals maintained on diets deficient in tryptophan (an important building block of proteins), vitamin E, and selenium. These studies have indicated that dietary deficiencies in tryptophan and vitamin E cause development of cataracts by a mechanism different from that causing cataracts

in animals fed a diet deficient in tryptophan alone. Recent research also indicates that diets that contain either too much or too little selenium can lead to an increased incidence of cataracts. Other studies of human senile cataract and selenium-induced cataracts strongly suggest that toxic oxygen metabolites, such as hydrogen peroxide, hydroxyl ions, or singlet oxygen, are triggering agents in the development of cataract. Attempts are being made to prevent or arrest cataract in animal models by using antioxidants.

### **Prevention of Blindness From Glaucoma**

The mechanisms by which glaucoma damages the optic nerve are being investigated by studying the effects of elevated pressure within the eye (intraocular) on several aspects of function at the optic nerve head. An attempt also is being made to identify factors other than intraocular pressure that influence the susceptibility of an optic nerve to damage from glaucoma.

The process by which elevated intraocular pressure causes the death of retinal ganglion cells is being investigated as are the potential causes for the increased susceptibility to glaucomatous damage found in aged, myopic, and black persons.

A study is being conducted to investigate important risk factors for the development of high intraocular pressure and glaucoma visual field defects. Attempts are being made to find an effective carbonic anhydrase inhibitor (CAI) for the treatment of glaucoma that could be applied topically to the eye in place of the currently prescribed systemic drugs, which have a number of undesirable side effects. CAIs are used in the treatment of some cases of glaucoma to decrease the inflow of aqueous humor to the eye, thereby reducing intraocular pressure.

A number of diseases have been linked to certain genetic defects or abnormalities. Research attempts to identify the exact expression of "incorrect" genetic information and to find ways to reprogram the gene or

to compensate for the error. Other often-inherited disorders are known as autoimmune diseases, in which chemical messages direct cells to turn against the body's own tissue.

### **Familial Hypercholesterolemia**

The 1985 Nobel Prize winning work by Drs. Michael Brown and Joseph Goldstein set out to understand the basic defect in familial hypercholesterolemia. Familial hypercholesterolemia is an inherited condition that can be passed on when either parent lacks an important receptor gene for the uptake and destruction of low density lipoprotein (LDL).

This trait occurs in about one in 500 individuals worldwide. Affected persons have elevated levels of LDL and cholesterol, a substance carried by the LDL. Cholesterol is deposited in arteries such as the coronary vessels and, as a result, coronary heart disease may appear, particularly in males between 35 and 50 years of age. When both parents have this trait, their children have a 25 percent chance of inheriting defective genes from both of them, a condition known as homozygous hypercholesterolemia (or excessive blood cholesterol caused by two identical genes). This event occurs once in a million births. Such children have extremely high LDL and cholesterol levels and usually have coronary heart disease in the teens or even earlier.

Brown and Goldstein astutely selected the very rare patients with homozygous hypercholesterolemia who had no normal genes at the site of the fundamental defect (at that time unknown) and discovered that cultured fibroblasts from these patients showed 40- to 60-fold higher activity of the enzyme that controls the rate of cholesterol biosynthesis (HMG-CoA reductase). This finding led to the discovery of the LDL receptor, which was non-functional or severely defective in these patients.

The discovery of the LDL receptor and its presence in many body cells, particularly the liver, revolutionized our understanding of cholesterol and lipoprotein metabolism. In a series of brilliant studies since 1974, each step in the pathway of

cholesterol through the cell was meticulously defined.

The mechanism of the intracellular LDL pathway now serves as a model for future elaboration of the physiologic action of the more than 20 receptors that are involved in mediating the uptake by cells of particles too large to diffuse through the cell wall (such as lipoproteins). The impact of this work on cell biology is enormous, since this function, known as receptor-mediated endocytosis plays a fundamental role in the growth, nutrition, and differentiation of all mammalian cells.

### **Genetic Marker for Huntington's Disease**

NIH conducted and sponsored an international research effort on this disease that led to the discovery of a genetic marker on Chromosome 4. This discovery has the potential to lead to identification of the specific gene of the full set of human genes that is defective. Such a finding enhances the probability of developing an adequate strategy for effective detection of Huntington's disease before symptoms develop. An appropriate preventive intervention may be developed when the actual gene has been isolated and cloned with genetic and biochemical techniques.

### **Inborn Errors of Metabolism**

Individuals with such inborn errors lack enzymes needed for the normal disposal of certain substances that are toxic if allowed to accumulate. Studies are being conducted to identify carriers of these diseases, to target enzyme therapy to appropriate nerve cell receptors, and to correct genetic deficiency through genetic engineering methodologies. NIH recently has succeeded in isolating, purifying, and storing enzymes deficient in Gaucher's disease, Fabry's disease, and Tay-Sachs disease, making these enzymes available for clinical enzyme replacement and for biochemical studies. As a result, genetic counseling is more precise. Cloning the gene responsible for deficient enzymes in Gaucher's disease has

been achieved, and technology is being explored to replace the defective gene with a normal one. Together with structural analysis of these enzymes, this work is yielding clues to guide the study of the mutations that lead to these deficiencies.

#### **Familial Defect Leading to Periodontitis**

A five-site study is investigating the familiar nature of relatively rare diseases that affect young people: juvenile periodontitis and prepubertal periodontitis (diseased gums). Both diseases appear to involve specific inherited defects in a critical infection-fighting white blood cell—the neutrophil. The findings point to a familial defect in the neutrophil's ability to move quickly to an inflammation site or swelling, where it normally kills invading microorganisms. This study also should aid in identifying individuals at risk for the diseases and in designing ways to correct this impaired cell function.

#### **Major Histocompatibility Antigens**

Basic research has been conducted into the several forms of the human major histocompatibility antigens. These are the antigens usually associated with acceptance or rejection of grafts and transplants by the recipient. Investigation has revealed that certain of these molecular entities are associated with chronic diseases of an autoimmune nature. Diseases that fall into these categories include insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, ankylosing spondylitis, and rheumatoid arthritis. Although these associations are not absolute, recent molecular studies are identifying particular portions of the antigen molecules which have very strong associations. Since these protein portions are inherited and are present from birth, it will be possible to devise simple tests to be performed on white blood cell extracts that will identify individuals who are likely to develop these diseases later in life. Early identification will lead to

early treatment of the disease and possible prevention of the numerous side effects that will result from delayed diagnosis.

#### **Prevention of Type I (Insulin-Dependent, Formerly "Juvenile-Onset") Diabetes**

Current research, which still requires many additional developments, aims at the hypothetical prevention of type I diabetes through prompt treatment with agents that suppress immune response early during the onset of the disease. Some evidence is accumulating that suggests that an autoimmune process is involved in the basic development of insulin-dependent diabetes. A current hypothesis holds that the autoimmune destruction of insulin-producing pancreatic cells could be counteracted and sufficient insulin production by the pancreatic cells could be preserved with the aid of an immunosuppressive regimen early in the course of type I diabetes, thus preventing progression to an irreversible insulin-dependent state.

Intense research may shed light on the cause, nature, and spread of more than one clearly related disease.

#### **Retroviruses and Cancer**

For years, the search for a retrovirus associated with human cancer had been unsuccessful. The discovery of T-cell growth factor in 1976 enabled the long-term culture of relatively mature T-cells, which in turn enabled the identification of HTLV in T-cell lymphoma cell lines. It is now possible to determine the course of events, starting with virus infection that induces these leukemias. The ultimate goal is successful intervention or prevention of the disease. The availability of HTLV-I also provides the unique opportunity to study precisely the epidemiology, that is, the frequency and distribution among populations, of adult T-cell leukemia (ATL) and related diseases and to identify some of these disorders as a single and unique clinical entity. The designation of AIDS as the number one national health priority by the Department

of Health and Human Services is based on both the rapid spread and the high lethality of this disease. Efforts led by NIH intramural researchers have demonstrated that a type-C RNA tumor virus, designated HTLV-III, is the causative agent of AIDS. The virus is largely confined to high-risk groups in the population. Some studies indicate that up to 20 percent of the African population may be virus-positive. AIDS is considered to be a sexually transmitted disease and, as such, could gain access into the general population. Consequently, the NIH is supporting a significant effort to develop an effective vaccine against the AIDS agent. To this end, it is encouraging basic research of the development and assessment of retroviral vaccines. Included in this research will be efforts to develop naturally occurring retrovirus animal models to evaluate systematically strategies for preparing substances that elicit immune responses, vaccination schedules, etc. Of particular importance will be basic studies to determine how retroviruses interact with and/or escape from the host immune surveillance system, characterization of retroviral components presumed to suppress immune response, efforts to enhance the immune response-producing capabilities of vaccine preparations, and the use of diverse modern approaches for the actual vaccine preparation.

At times research findings will provide benefits beyond the scope originally envisioned by investigators.

#### **Use of Mussel Adhesive Protein in Dentistry**

Findings from a decade of research supported by the NIH are about to revolutionize dentistry. A remarkable adhesive protein has been isolated from mussels and reproduced. This rapid-acting "superglue" anchors the mollusks to virtually any underwater surface, including rock, metal, glass, wood—even to another shellfish—and holds potential for a broad range of practical applications. In dentistry, for example, the protein adhesive could be used as a



decay-preventing sealant or to repair dental caries by gluing fillings into teeth with minimal drilling. It also may have properties superior to dental cements currently available, for cosmetic applications such as securing crowns and bridges, and for repairing fractured teeth. Mussel glue has a potential role in periodontal surgery—aiding the healing process by creating a strong bond between gum tissue and teeth. It is expected that the adhesive will be available for feasibility studies of dental uses within 2 years. Scientists now are exploring recombinant DNA technology to produce the protein in large quantities. Widespread medical and industrial uses also are expected to be found for mussel glue.

### **Applied Research and Clinical Investigation**

Applied and clinical research takes the findings of basic investigations and uses them to find safe and effective means to detect and treat disease, to identify at-risk populations, and to further understanding of the causes of disease. It begins to test possible methods of preventing diseases or halting their progression. Many applied and clinical studies investigate the factors that can contribute to disease prevention.

Among applied and clinical studies supported by the NIH are those that expand our knowledge about the relationships of the foods we eat to health and disease status.

### **Diet and Nutrition**

A number of epidemiologic and experimental studies suggest that about 35 percent of cancer mortality is related to dietary factors. For example, some vitamins and minerals (micronutrients) such as vitamin A and its precursor, beta-carotene; synthetic retinoids; vitamins C, E, and B<sup>6</sup>; folic acid and the trace mineral, selenium, may protect against certain types of cancer. A number of clinical trials are now under way to test these agents in various populations at high risk.

Similarly, diets high in total fat calories are associated with cancers

of the breast, colon, rectum, uterus (endometrium), and prostate. High intake of dietary fiber, on the other hand, is associated with lower risk for colon and rectal cancers. Dietary studies directed at exploring these relationships now include clinical trials of low fat diets in women at increased risk for breast cancer, a study to develop an International Food Composition Data System to enhance the quality, quantity, and accessibility of nutrient and non-nutrient data, study on the physico-chemical effects of dietary fiber and studies to develop methodologies for detecting and quantifying fiber in everyday foods.

### **Prevention of the Emergence and Progression of Noninsulin-Dependent Diabetes Mellitus (Type II)**

Generally speaking, persons at risk are obese individuals with a strong family history of type II diabetes. In the United States there are about 5 million known patients with type II diabetes; epidemiologic data indicate the existence of another 5 million individuals with the disease as yet unrecognized. Emerging research evidence suggests that weight reduction, attainment of lean to optimal body weight, adherence to sound diets, and regular physical exercise will reduce the metabolic abnormalities and clinical symptoms in most patients with this type of diabetes. The NIH diabetes program supports a broad range of research to define the relationship between body weight, exercise, and diabetes and to determine whether lifelong maintenance of normal body weight and physical fitness can prevent the development of noninsulin-dependent diabetes.

### **The Effects of Weight and Diet on Hypertension**

NIH-funded investigators conducting a collaborative study on the dietary treatment of high blood pressure have reported that weight loss or sodium restriction can retard the return of high blood pressure in patients who have achieved normal blood pressure levels through drug treatment. Patients in the intervention group included those for whom weight loss of 10 pounds

was the goal and those for whom a specified daily reduction of sodium was prescribed. Control groups received no dietary intervention. Over a period of 56 weeks, the patients in the intervention groups were more than twice as successful as those in the control group in maintaining normal blood pressure.

NIH-supported researchers at the University of Michigan recently reported findings that may be valuable in preventing obesity-related hypertension in juveniles. The finding resulted from a project to determine the role of aldosterone, a sodium-regulating hormone, in the regulation of blood pressure in obese adolescents. The researchers report that obese adolescents apparently have higher levels of both aldosterone and blood pressure than nonobese adolescents, and that weight loss reduces the differences between these two groups. Both aldosterone and blood pressure seem to follow weight status in adolescents. The work could lead to important insights into the prevention of obesity-associated hypertension in adolescents.

### **International Prevention Efforts**

Among prevention-related activities that resulted from some of the 56 bilateral agreements with 31 countries are several typical of those identifying disease and health factors:

- Long-term, ongoing studies supported by the NIH and conducted in three developing countries—Guatemala, Bangladesh, and India—have shown that a mother's nutritional status before she conceives and the amount of weight she gains during pregnancy have an important impact on pregnancy outcome. When other factors such as maternal age, the number of children previously borne, and socioeconomic status are held constant, women who weigh more before conception and gain more weight during pregnancy are more likely to have a live birth.

- U.S. and Japanese scientists, working collaboratively under NIH sponsorship, published important

new findings on relationships between dietary protein and the incidence of hypertension and stroke. Results derived from research using a strain of genetically stroke-prone, spontaneously hypertensive rats indicate that modification of dietary protein influences the calcium metabolism of heart muscle and, indirectly, the development of hypertension. This research has provided one of the few clues to the biochemical basis of hypertension.

Other studies seek to identify environmental agents that increase the risks for particular diseases, to improve our methodology for predicting the adverse health effects of environmental agents, and to characterize the mechanisms by which these agents contribute to disease.

#### **Toxicity Studies of Environmental Chemicals**

Our knowledge in the environmental health sciences is advancing, but large numbers of chemicals exist in the environment that may have public health significance and for which there is minimal or no information available for use in health risk assessment. Largely through the Department's National Toxicology Program (NTP) which NIH administers, the agency supports efforts to improve the sensitivity and reliability of methods for predicting adverse health effects caused or aggravated by environmental chemicals and to apply a comprehensive approach to toxicological testing so that numerous endpoints or potentially toxic effects are examined. These NIH/NTP toxicological testing efforts, in conjunction with NIH intramural and extramural activities focused on developing a better understanding of the mechanisms of hazardous agents and extrapolating from laboratory data to humans, have resulted in increasing research emphasis being placed on defining structure-activity relationships for the toxic actions of chemicals. Because of these efforts, the sequence of biochemical events ultimately leading to manifestations of toxicity is becoming clearer for some chemicals.

#### **The Effects of Environmental Agents on Development**

In recent years, the NIH has been broadly concerned with the influences of drugs and ultrasound radiation on development, primarily because of their suspected potential for the causation of abnormalities to offspring in the uterus (human teratogenicity). For example, recently a grave concern erupted over the use of vitamin A and its structural analogues for the treatment of dermatologic conditions and precancerous disease. Also, an observation has been made linking maternal treatment with a vitamin A retinoid during the first trimester of pregnancy to spontaneous abortions and birth defects. NIH studies in this area have now shown that certain structural modifications of the vitamin A molecule, such as changes in its ring or side chains, can alter retinoid teratogenicity. These structural and activity relationships, along with placental permeability and tissue distribution of retinoids, are being determined in order to allow for improved clinical retinoid therapy in oncology and dermatology.

The widespread use of ultrasound in the evaluation of pregnancies is another concern of the NIH. About one-third to one-half of all pregnant women and therefore at least one million developing fetuses, are exposed each year to ultrasound. Therefore, currently supported animal studies are being used to evaluate irradiated fetuses through prenatal development and into postnatal life to determine all possible adverse developmental outcomes of ultrasound exposure. In particular, the NIH places special emphasis on the risk of malformations of the neurological and cardiovascular systems.

#### **The Effect of Chlorinated Drinking Water and Other Factors on Atherosclerosis**

Studies in several species of animals have shown that chlorinated drinking water elevates blood cholesterol levels. The mechanism of the effect, if real, is unknown. However, because cholesterol is an important risk factor for atherosclerosis (narrowing of the arteries)

and because of the universal exposure to chlorine in our environment, it is important to discover whether such an effect exists in humans.

Research scientists at the University of Cincinnati General Clinical Research Center, in cooperation with the Environmental Protection Agency, are conducting a controlled clinical trial to discover whether chlorinated drinking water raises human serum cholesterol. Twenty subjects eventually will be studied in the trial, and multiple safety tests will be conducted throughout. Several subjects have completed the trial, but results are too preliminary to draw conclusions.

#### **Risk Factors for Diabetic Retinopathy**

A case-control study is being conducted in diabetic patients to identify and evaluate risk factors for development of diabetic retinopathy, a disease of the retina of the eye, patients are being asked questions about medical and social factors (e.g., family history, smoking habits, beverage consumption, etc.) which may be associated with the development of retinopathy. Blood specimens from these patients also are being evaluated for systemic and metabolic factors that may play a role in the development of retinopathy. It is expected that this information will allow the evaluation of the predictive value of the risk factors identified.

#### **Immediate Response to Environmental Emergencies**

Because of the inherent flexibility of certain grants, NIH can turn to its centers to respond to emerging environmental health research needs and problems. NIH also responds to the need for intervention, as in environmental emergencies, by providing scientific information necessary for developing effective intervention measures. For example, following the accidental release of methylisocyanate (MIC) from a pesticide manufacturing plant in Bhopal, India, NIH developed and implemented a series of studies designed to examine the long-term health effects of acute short-term



exposure to the chemical.

Many questions remain to be answered about the diseases of aging. Among a variety of studies in this area are several that seek to reduce the risk for bone damage in the elderly caused either by osteoporosis or by falls.

### **Advances in the Prevention of Osteoporosis**

In recent studies to determine the degree to which estrogen deficiency alone or aging alone is responsible for postmenopausal bone loss, each woman of a group of 14 whose ovaries had been surgically removed (oophorectomy) was matched for age and years since menopause with two normal control individuals, one near the time of menopause (perimenopausal) and one postmenopausal. The density of bone mineral was determined by special radiologic techniques (absorptiometry). Results showed that the perimenopausal group, at the same average age as the oophorectomy group, had normal bone density; the other two groups had significant density losses. The postmenopausal group, combining the effects of age (20 years older) and lack of estrogens, had only slightly more bone loss than the oophorectomy group. It was estimated that three-fourths or more of the bone loss in those patients was due to estrogen deficiency rather than to aging. The rapid bone loss induced by menopause is assumed to be superimposed on a slower bone loss process related to aging (which is likely analogous to the process causing bone loss in older men).

In another study, the same group of investigators found that calcitonin, the thyroid hormone often said to be involved in postmenopausal bone loss, is actually present in normal amounts in untreated osteoporosis, and that the gland is able to respond by secretion of calcitonin when stimulated by calcium. This finding gives added significance to the role of estrogen deficiency in the causation of osteoporosis.

### **Prevention of Falls by Older Persons**

Accidents, including falls, are one of the leading causes of death in older persons. It is estimated that each year, one out of every three persons over age 65 suffers a fall. A study of accidental falls in the elderly being conducted by the Center for Health Research at Kaiser Permanente in Portland, Oregon, and partially supported by NIH, holds promise for providing much needed information on falls and their prevention. Included in the study is a home safety audit and improvement program designed to identify and remove external risk factors for falls and screening and treatment for visual problems that may contribute to increased falls. In addition, the NIH has issued a request for applications focusing on research relative to age-associated neurologic and cardiovascular dysfunctions associated with falls.

Vaccination is one of our oldest methods of disease prevention. Although the methodology for vaccine production is well known, not all disease organisms can be broken down easily into subunits from which vaccines can be safely and efficaciously produced. Thus, viral and bacterial diseases still remain to be prevented through vaccine development.

### **Accelerated Development of New Vaccines**

The NIH initiated this program in 1981. To assist in planning, the Institute of Medicine (IOM), National Academy of Sciences, was chosen to develop a model decision process that could be used for establishing priorities among vaccine candidates. The IOM study was divided into two major phases, one for the development of a model system for the examination of vaccines for domestic use, and the second for international use. Volume I of the IOM Report ("New Vaccine Development: Establishing Priorities, Diseases of Importance to the United States") was published in 1985; Volume II ("Diseases of Importance in Developing Countries") has been completed and will be published in mid-1986.

For domestic use, the IOM analysis assigned the highest priorities to the following five vaccines:

- Hepatitis B virus (recombinant DNA-derived)
- Respiratory syncytial virus (live attenuated)
- Haemophilus influenzae*, type b
- Influenza (live attenuated)
- Varicella (chicken pox) (immunocompromised children)

For international use, the IOM analysis assigned the highest priorities to the following five vaccines in the order listed:

- Streptococcus pneumoniae* (protein-polysaccharide conjugates)
- Rotavirus
- Malaria (*P. falciparum* sporozoite)
- Salmonella typhi* (typhoid)
- Shigella (bacillary dysentery)

An improved pertussis (whooping cough) vaccine already had been assigned high priority by NIH, so pertussis was not ranked by the IOM.

Encouraging progress has been made in the development of vaccines for a number of these disease-causing agents, as follows:

- A number of acellular pertussis vaccines now have been developed by U.S., European, and Japanese manufacturers. Two Japanese-produced acellular pertussis vaccines are being tested for efficacy in an extensive field trial in Stockholm, Sweden, with support from NIH and USAID. Other improved pertussis vaccines are to be tested soon in NIH-supported Vaccine Evaluation Centers. A *Haemophilus influenzae* type b vaccine for the prevention of meningitis, epiglottitis, and pneumonia in children 2 years of age and older has been licensed and is produced and marketed by three manufacturers. An *H. influenzae* type b vaccine for use in children under 2 years of age is being tested for efficacy in native Alaskan children.

- A live attenuated varicella virus vaccine has been shown to be safe and effective for the prevention of chickenpox in children with acute leukemia whose immune systems

had been suppressed as part of their treatment and, more recently, in normal children. Licensing is anticipated shortly.

• Hepatitis B is the most common cause of hepatitis in the United States and a common cause of chronic hepatitis and liver cancer worldwide. Over the past 10 years, a vaccine against hepatitis has been developed, largely through the work of NIH scientists. Despite development of a safe vaccine, hepatitis remains a serious problem, partly because the vaccine is expensive. Using recombinant DNA and other new technologies, second-generation hepatitis vaccines have been developed more economically and tests have shown them to be safe and to produce immunity against hepatitis B virus.

#### **Development of a Herpes Simplex Vaccine**

An experimental herpes vaccine that not only counters an immediate herpes simplex virus attack, but also prevents the virus from establishing a latent, recurrent infection, was developed last year by a team of researchers from two NIH institutes. The vaccine, which has been tested successfully in laboratory mice, is targeted against herpes simplex virus type 1 (HSV 1), the organism responsible for oral cold sores. The vaccine, however, also appears to provide substantial protection against HSV 2, the cause of genital herpes. Now, 1 year later, scientists have shown that the vaccine continues to provide immunity in animals. This is the first demonstration of the duration of effectiveness of a recombinant herpes vaccine and gives further impetus to animal testing in anticipation of human trials.

#### **Generic Development of a Vaccine for Malaria**

Malaria afflicts approximately 300 million persons worldwide. It is a debilitating disease that is fatal in many cases, especially in children. Control efforts directed against the mosquito carrier have been unsuccessful due to its developing a resistance to the insecticides being used. In addition, there has been

an increasing prevalence of drug-resistant parasites in several areas of Africa and Southeast Asia, with a resultant upsurge in cases of malaria. The need for an effective vaccine has become evident and the new technologies of recombinant DNA and monoclonal antibody production have made such an advance possible. NIH intramural scientists have described the characteristics of the major protein antigen of sporozoites, the stage transmitted by the mosquito. Genes coding for the protein have been cloned and antigens based on repeating subunits of the protein have been produced by recombinant DNA or as synthetic peptides. Two vaccines have been prepared commercially and are presently being tested in human volunteers for safety and immunogenicity.

Knowledge may enable us eventually to prevent acute onset of diseases, such as stroke. When it is not yet possible to prevent the disease itself, efforts are made to prevent or control some of its disabling side effects.

#### **Prevention of Stroke**

In a recent international controlled clinical trial, an NIH-supported study has demonstrated that the extracranial/intracranial (EC/IC) bypass brain operation is no more effective and less safe than medical therapy in preventing stroke or stroke death. Thus, it should be abandoned for safer and equally effective medical alternatives. In addition, NIH is aggressively studying stroke and its causes. In focusing on specific stroke-prevention studies, scientists are exploring the use of medical and surgical interventions in acute cerebral infarction, acute ischemia, cerebral arterial spasm after subacute hemorrhage, acute stroke, cerebral infarction, transient ischemic attack (TIA), and the proper timing of surgery to prevent hemorrhagic stroke in brain aneurysms.

#### **Coronary Angioplasty**

More and more patients are undergoing percutaneous transluminal coronary angioplasty (PTCA) to relieve coronary artery obstruction. The procedure dilates

the narrowed segments of the arteries with a balloon that is inserted into a peripheral vessel and threaded toward the heart. PTCA can relieve angina pectoris (chest pains) in a patient and improve exercise tolerance and left ventricular function. However, in 20 to 30 percent of the cases, restenosis (recurrent narrowing) occurs—making it necessary for the patient to restrict activities, resume antianginal medications, undergo a repeat PTCA procedure, or have bypass surgery. A trial at the Mayo Foundation is testing the hypothesis that therapy with the drug dipyridamole plus aspirin can reduce the incidence of restenosis.

#### **Reduction of Arterial Plaque**

On another front, researchers at Stanford University, using Biomedical Research Technology Program-supported laser center resources, are conducting investigations into the development of laser technology for reducing cholesterol plaque in the arteries. Through initial studies, they have defined the necessary energy density to vaporize the plaque effectively. However, there are technological problems involved in delivering the necessary amount of energy down the fiber optics currently available. Now their efforts are directed toward testing various wavelengths that may be easier to transmit, and toward developing nontoxic dyes that would enhance the laser's action on plaque while leaving normal tissue undamaged.

#### **Chemoprevention of Multiple Sclerosis**

Multiple sclerosis is a chronic progressive or relapsing/remitting disease of the central nervous system which interferes with movement, speech, and vision. It affects females more than males and whites more than blacks. In 1976, it was diagnosed in 4 of every 100,000 persons (incidence) with 58 of every 100,000 people having MS that year (prevalence). These NIH data provide the first scientifically reliable baseline estimates of incidence and prevalence of this disease. A pilot clinical trial with Copolymer I

showed some promise that this drug may prolong remission periods or reduce relapses, thereby preventing disability in treated versus control groups. Further trials will be needed to confirm this preliminary evidence.

#### **Prevention of Diabetic Retinopathy**

A clinical trial, the Early Treatment Diabetic Retinopathy Study (ETDRS), is being conducted to test the effectiveness of argon laser treatment in people whose diabetic retinopathy (disease of the retina of the eye) has not progressed far enough to pose an immediate risk of blindness, that is, those with a swelling of scar tissue on the cornea known as macular edema, preproliferative retinopathy, and mild or moderate proliferative retinopathy. Initial findings from the ETDRS indicate that focal argon laser treatment (using the laser to coagulate only that tissue which is suspected of leaking fluid into the macula and causing macular edema) decreased the amount of vision loss and the frequency of persistent macular edema, increased the chance of vision improvement, and caused only minor visual field losses when compared to an untreated group. These findings have led the ETDRS investigators to recommend foveal photocoagulation treatment in all eyes with significant macular edema and nonproliferative retinopathy.

#### **Prevention of Blindness From Glaucoma**

A multicenter randomized clinical trial is being conducted to assess the efficacy of argon laser trabeculoplasty, a treatment that administers a series of laser burns to the trabecular meshwork (the area through which the aqueous humor leaves the eye) to lower the intraocular pressure, as an alternative to standard medical therapy for open-angle glaucoma. Reduction of the intraocular pressure may prevent further damage to the optic nerve and associated vision loss.

A multicenter randomized clinical trial also is being conducted that seeks to improve the prospects of conventional glaucoma surgery by the administration of the antimeta-

bolite, 5-fluorouracil. Surgical failures result when scar tissue forms over the site of a tiny incision made to let minute amounts of aqueous humor leave the eye in order to lower intraocular pressure. Preliminary studies have shown that 5-fluorouracil, an agent which inhibits scar tissue formation, was of benefit in high-risk surgical patients. This should allow the continued lowering of intraocular pressure and prevent additional damage to the optic nerve.

#### **Relief of Porphyria with LHRH Analogue Therapy**

Porphyria is an acute intermittent genetic disease. It is expressed in affected women by recurrent and frequent premenstrual attacks that are severely disabling. Certain physiological factors, such as steroid hormones and their metabolites, are known to promote or worsen the symptoms of the disease. In particular, women who take steroid-containing contraceptives are at risk for an increased severity of the disease's expression. Women who do not practice birth control are faced with the risks of the expression of the disease and its symptoms to themselves as well as the resultant genetic consequences of pregnancy to their fetuses. Until recently, therapeutic management to prevent premenstrual porphyric episodes was misleading, with benefit to some and provocation of attacks in others. An exciting insight into a potentially beneficial therapy recently has been reported by NIH-supported scientists who found that a long-acting analogue of a specific peptide, LHRH, provided by another NIH-supported project, successfully alleviated cyclical premenstrual attacks of porphyria in a severely affected patient. Treatment resulted in the cessation of attacks along with absent menses, persistently lowered progesterone levels, and decreased follicle-stimulating hormone levels. These findings were consistent with the known inhibitory effect that the analogue has on reproductive function, that is, the blocking of ovulation. The use of the analogue for

therapy is also attractive because it has the feasibility of long-term field administration via intranasal spray delivery and only minor acute side effects have been noted. While further studies are needed to discern responders from nonresponders within the genetically affected population, the results reported present an exciting potential for both the alleviation of premenstrual-provoked episodes of porphyria and an appropriate alternative birth control method for these patients.

Similar to attempts to minimize the side effects of disease are efforts to diagnose diseases in their earliest stages so that illness and death can be diminished.

#### **Cancer Screening and Detection**

Screening and early detection of cancer is recognized as having significant potential for reducing illness and death. Before implementing screening and early detection as public health measures, however, there are many research questions that must be addressed. For example, is the screening modality sufficiently safe; can it be adequately performed with optimal quality assurance in the general population; and does the measure have adequate sensitivity, specificity, and predictive value to be of benefit with respect to cost and risk?

A phase III controlled clinical trial is being conducted to determine if screening for hidden blood in the stool will reduce mortality from colorectal cancer. Final results from the trial are expected in 1990.

The Breast Cancer Long-Term Followup Study has been completed and analysis of the data is under way. Additional followup is planned to gain more information on the natural history of the disease and long-term impacts of breast cancer screening.

#### **Acquired Immune Deficiency Syndrome**

Several NIH-supported investigators have now identified specific oral lesions that may precede the clinical picture of AIDS. Recent studies confirm for the first time that the unusual oral lesion, hairy leukoplakia (HL), is clearly a marker in many patients. This new finding

underscores the importance of regular examinations for oral tissue changes in high-risk groups, and the need for dental professionals to be alert to the possible presence of oral lesions in their patients.

### **Intervention Studies**

Intervention studies seek to determine whether the act of intervening with therapy, screening, or education will make a difference in the disease process. Such studies also are undertaken to demonstrate whether or not the planned method of intervention can be carried out feasibly and cost effectively in large populations. The following examples provide a cross-section of NIH-supported intervention studies.

#### **Smoking and Health**

Given the mortality burden in cancer, cardiovascular, and lung disease from smoking and tobacco use, several Institutes are directing resources to study a number of issues related to the smoking problem. Of particular note are the large-scale intervention efforts being directed to reduce smoking and tobacco use prevalence. More than 40 controlled intervention trials are under way that are testing prevention and cessation strategies in adolescents, minorities, women, heavy smokers, and smokeless tobacco users. The major strategies under examination involve the media, schools as sites for prevention in adolescents, the worksite, self-help procedures, and the use of physicians and dentists as interveners.

#### **Lowering Risk for Cardiovascular Disease**

NIH is supporting three major community-based research and demonstration studies, specifically, the Stanford Five-City Project, the Minnesota Heart Program, and the Pawtucket (RI) Heart Health Program. These programs are testing the feasibility and effectiveness of community-based programs directed at lowering the risk of cardiovascular illness and death. All three of these large field studies are conducted by multidisciplinary research

teams and are addressing the risk factors of blood pressure, smoking, cholesterol, physical inactivity, and weight. All are using multiple theoretical models for behavior change (e.g., community organizations) and multiple strategies and approaches. The three studies emphasize to a varying degree the use of print and other media, and youth programs are a part of each program. The studies are using quasi-experimental design and employ multiple approaches for evaluation, including formative and process evaluation, cross-sectional and cohort surveys, program contact tracking systems, and morbidity and mortality surveillance. These long-term, ongoing studies have received a great deal of attention and are regarded as major national efforts to provide a model for community programs in the area of disease prevention and health promotion.

#### **Reducing the Rate of Progression of Chronic Renal Disease**

Each year, many thousands of patients who have been afflicted with a variety of chronic diseases of the kidney reach a point in the downhill progression of their disease where they develop clinical symptoms of kidney failure and become uremic. Uremia, a toxic condition caused when the kidneys can no longer process the excessive products of protein metabolism, is the final, common pathway of progressive renal failure. It is irreversible and ultimately fatal unless the patient enters a program of thrice-weekly dialysis treatments or receives a kidney transplant (if a suitable organ is available). Any treatment that prevents (even temporarily) the development of end-stage renal failure and postpones significantly the need for dialysis therapy would be a vast improvement for these patients. Past experiments have indicated that, in many cases, a strictly adhered-to low-protein, low-phosphate diet can be effective in retarding the development of symptomatic uremia. The NIH has initiated a large, controlled, multicenter clinical trial in order to determine if dietary therapy can retard the progression

of chronic renal failure, and if dietary protein restriction (if found effective) is nutritionally safe in patients with progressive renal failure.

#### **Prevention of Insulin-Dependent Diabetes Mellitus (Type I)**

This grave disease requires daily administration of insulin to keep the patient alive. Even though this treatment has extended the average lifespan and improved the quality of life of patients with type I diabetes, it has not prevented the development of the chronic progressive degenerative changes in various tissues that lead to heart attacks, strokes, kidney failure, gangrene, blindness, and damage to the nervous system. Most of the illness, death, and economic cost associated with diabetes is due to these degenerative tissue changes. There is a longstanding, unresolved controversy over whether strict and precise control of blood glucose levels in persons with diabetes will prevent these life-threatening degenerative changes. Recently developed technologies permit, for the first time, studies to assess whether "tight" metabolic control will prevent the diabetic complications. As a result of these advances, the NIH has initiated a large, collaborative clinical trial on the relationship between blood glucose control and the vascular complications of diabetes mellitus. This multicenter clinical trial will continue for the next 7 years. Its outcome will yield much needed information concerning the possible prevention of the serious, disabling, and life-threatening clinical complications of type I diabetes.

#### **Reducing Morbidity Associated with Maternal PKU**

Phenylketonuria (PKU) is caused by an inborn error of metabolism, resulting—unless treated—in mental retardation, neurologic disorders, and other side effects. Over the past 20 years, female infants with PKU receiving early dietary treatment have reached normal physical and intellectual development. Many of these women have already reached, or are approaching, the childbearing period. Recent observa-

tions of such women with PKU, who are maintained on a regular diet during pregnancy, have found them to be at a high risk for bearing children with abnormally small heads (microcephaly), mental retardation, congenital heart defects, and intrauterine growth retardation. In addition, animal studies suggest that a level of phenylalanine that is safe for the mother may be detrimental to the health of the developing fetus (it is an accumulation of the amino acid, phenylalanine, that causes PKU). These observations prompted the NIH to initiate a collaborative project to evaluate the efficacy of a phenylalanine-restricted diet in reducing morbidity associated with maternal PKU. Four contributing centers and one coordinating center are participating in this prospective, longitudinal, and observational study. The study involves all 50 states, the District of Columbia, and Canada. Specifically, this cooperative study seeks to determine: the level of maternal phenylalanine that will maintain a normal pregnancy; the stage of pregnancy at which a low-phenylalanine diet is most effective in preventing the effects of maternal PKU on the developing fetus; whether initiation of the diet before rather than after conception improves the baby's outcome; whether the diet reduces the frequency of mental retardation and other complications found among infants of PKU mothers; and the effect that the maternal blood levels of tyrosine and such micronutrients as zinc have on the outcome of pregnancy.

#### **Reducing Problems of Aging**

A number of clinical problems of older people such as incontinence, osteoarthritis, stroke, falls, and hip fractures have received little research attention from the medical community although they represent major causes of chronic disability and institutionalization. Their prevention and treatment may be possible through a better understanding of the underlying disease processes and related factors. One

such clinical problem is urinary incontinence, a significant cause of disability and dependency among the elderly. Urinary incontinence may affect as much as 10 percent of the older population and may significantly restrict their activities. As part of a behavioral medicine program, NIH intramural scientists have operated an outpatient clinic for research on behavioral interventions to treat fecal and urinary incontinence in elderly patients. An inpatient program has been initiated to enable the further assessment of the techniques, their utility in a patient population typical of nursing home residents, and the capacity of nursing staff to administer them effectively. The Health Care Financing Administration shares the cost of this project with NIH. In addition, five clinical trials of behavioral therapies for urinary incontinence are jointly supported by NIH and the Division of Nursing of the Health Resources and Services Administration. The behavioral therapies being studied include habit retraining, bladder training, pelvic floor exercise, and biofeedback approaches.

#### **The Success of One School-Based Fluoridation Program**

Nelson County, Virginia, operates the oldest school-based fluoride program in the country. Fourteen years ago NIH initiated the program, in which school children receive daily fluoride tablets, use weekly fluoride mouth rinses, and use a fluoride dentifrice. When the program was begun in 1972, only 15 percent of the children were caries-free. Eighty-five percent had at least one tooth that was decayed, had been filled, or had been pulled because of decay. Almost 30 percent had 11 or more decayed, missing, or filled teeth. Part of the problem was that the drinking water in the county has a very low concentration of fluoride. To date, the results have been impressive. There has been a 65 percent overall decline in tooth decay among the area's youngsters. Today 40 percent of Nelson County school children are caries-free, and only 6 percent have 11 or more decayed, missing, or filled teeth.

## **Professional and Public Prevention Education**

There are a number of NIH programs of relevance to prevention that feature interaction with the scientific and public health community, health providers, and consumers. The following describe selected educational activities.

#### **National Cholesterol Education Program**

After the findings of the Coronary Primary Prevention Trial (January 1984) and the recommendations of the NIH Consensus Development Conference panel on lowering elevated blood cholesterol (December 1984), the NIH launched the National Cholesterol Education Program by holding its first Coordinating Committee meeting in November 1985. The committee comprises more than 20 national medical, public health, and voluntary organizations, which have combined in an attempt to reduce cardiovascular illness and death with a national effort aimed at lowering elevated blood cholesterol in the United States. An expert panel has been convened to develop detailed recommendations as to the proper treatment of high blood cholesterol. Another panel was convened to address the problem of laboratory standardization as a means of enhancing the accuracy and reliability of blood cholesterol measurements. Several physician education efforts have been launched by the program or by others collaborating with the program, and a mass media campaign urging the public to "know your cholesterol" is now under way. The program will draw heavily upon the high blood pressure model and will develop partnerships and networks of public and private sector groups to carry educational messages to professional and public audiences and to stimulate activity that would enhance improved detection and treatment of high blood cholesterol.

#### **D.C. Better Babies Project**

Since 1984, the NIH has taken the lead in a 3-year research and demonstration effort to reduce the

rate of infant mortality and illness associated with low birth weight in a specific high-risk area of the District of Columbia. The project, called the Better Babies Project, involves collaboration with the Greater Washington Research Center, and the City Health Department. It attempts to identify as early as possible all pregnant women in the target area and to encourage them to begin prenatal medical care, improve the frequency and total number of their prenatal visits, improve adherence to health and medical advice, and link them to other medical and social services, such as interventions to address smoking and drinking habits and nutritional needs. In addition, training is offered to help them recognize early signs of premature contractions in an effort to diagnose premature labor at a time when it still can be prevented. The impact of the interventions will be evaluated by measuring the rate of low birth weight for all women in the target area and by comparing these findings to other areas of the city that are comparable in population composition and in risk of low birth weight. The project is unique in that the study is designed to circumvent the problem of self-selection, where evaluation of the impact of services is measured only by the participants in the program. Furthermore, this project will help to qualify the effectiveness of a prevention strategy designed to reduce the number of low birth weight infants and preterm labor.

#### **Cancer Prevention Awareness Program**

This program represents an effort to increase public awareness of the possibilities for cancer prevention, to present information to Americans on what they can do on a daily basis to control their own cancer risks, and to encourage people to adopt healthful behaviors to reduce individual risks of cancer. Messages are directed to the following risk factors: tobacco, alcohol, diet, radiation, estrogens, occupational exposures, and viruses. Phase I activities are directed as messages developed for the general public and are being

disseminated primarily through mass media channels. Phase II activities are directed to target audiences at greater than average risk for any of the selected cancer risk factors.

#### **Acquired Immune Deficiency Syndrome**

Since the fall of 1983, the NIH has been supporting and facilitating Regional Conferences on AIDS across the Nation. NIH staff and support contractors have worked closely with local organizing committees to structure an informative program that would be responsive to local concerns. The audiences have been mostly physicians, nurses, other health care workers, and members of public service organizations. In most regions, provisions also were made to provide information for the general public—either by encouraging their attendance at medical sessions or, preferably, by organizing special sessions to address their concerns with the appropriate level of scientific material.

#### **Asthma**

NIH-supported grantees have developed programs for the self-management of asthma. The Asthma Care Training (ACT) program developed at UCLA in conjunction with the Asthma and Allergy Foundation of America has been distributed to 35 communities throughout the United States, where it currently is being used by children and their families. The NIH also sought the collaboration of the American Lung Association and its network of state and local affiliates where private funding was obtained for disseminating information and conducting workshops. These efforts constitute a notable success in altering the quality of life for the victims of a major childhood disease through effective education. They have resulted in earlier intervention designed to avoid life-threatening situations and reduce the number of hospitalizations. This is especially effective for children who do not have private physicians in that it provides a level of education con-

#### **NIH Prevention Research (Dollars in thousands)**

	1985 Actual
Cancer .....	\$ 322,165
Heart .....	145,532
Dental .....	27,498
Diabetes .....	90,544
Neurology .....	38,395
Allergy .....	55,906
General Medical .....	2,929
Child Health .....	118,957
Eye .....	39,279
Environmental Health .....	163,124
Aging .....	84,834
Arthritis .....	36,905
Research Resources .....	32,549
Fogarty .....	5,261
Total, NIH .....	\$1,163,878

*Prevention research includes research that is designed to yield results directly applicable to interventions to prevent disease or the progression of presymptomatic disease. Included are studies aimed at elucidating the chain of causation—the etiology and mechanisms of acute and chronic disease.*



cerning their disease not ordinarily available in the usual community health care setting.

#### Diabetes and Periodontal Disease

The results of recent NIH-supported studies have established a pathological relationship between periodontal (gum) disease and diabetes mellitus. With early diagnosis and prompt treatment, however, oral health—and diabetic control—can be maintained. This is the message of a new exhibit recently designed to inform the medical, dental, and diabetes communities about this major complication. The exhibit also serves as a focus for the distribution of a new diabetes-targeted publication developed by NIH entitled "Detection and Prevention of Periodontal Disease in Diabetes." The booklet is a basic, informative guide for primary care physicians and allied health professionals who work with diabetes patients.

#### Multipurpose Disease Centers

These NIH-supported centers have education and demonstration components featuring information, continuing education, and training programs for medical and allied health professionals and for patients. Of particular importance to prevention are programs of education and dissemination of information for the general public concerning the risk factors associated with specific diseases, the importance of early diagnosis and treatment, and discouragement of the use of unapproved and ineffective treatment measures.

#### FY 1986 Prevention FTEs\*

<u>Institute</u>	<u>FTE</u>
NCI	704
NHLBI	76
NIDR	97
NIDDK	111
NINCDS	66
NIAID	114
NIGMS	—
NICHD	136
NEI	5
NIEHS	552
NIA	207
NIAMS	19
DRR	—
FIC	1
TOTAL	2,088

*\*Due to the variability of organizational and program structure within the twelve individual bureaus, institutes, and divisions comprising the NIH, it was not possible to arrive at a uniform method for estimating FTEs assigned to prevention activities; consequently, it was necessary to employ a number of approaches in arriving at a total estimate.*



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# **Section**

## **4**

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**Biennial Reports  
of the  
NIH Institutes  
and Research  
Divisions**

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# Biennial Reports of the NIH Institutes and Research Divisions

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## Introduction

Section 407 of the Health Research Extension Act of 1985 requires that "The Director of each national research institute, after consultation with the advisory council for the institute, shall prepare for inclusion in the biennial report made under section 403 a biennial report which shall consist of a description of the activities of the institute and program policies of the Director of the institute in the fiscal years respecting which the report is prepared."

Pursuant to section 407, the following segment contains the biennial reports of the NIH Institutes and Research Divisions. Each report provides (1) a description of the mission, history, and organizational structure of the Institute; (2) a discussion of areas of scientific opportunity and recent research advances; (3) an indication of program priorities; (4) a discussion of planning issues facing the Institute; and (5) a discussion of new initiatives and future program directions.

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## The Biennial Report of the Director, National Cancer Institute

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### History

The following events represent milestones in the development of the National Cancer Institute (NCI).

- August 5, 1937—The National Cancer Institute was established by the National Cancer Institute Act.
- July 1, 1944—The Public Health Service Act (P.L. 78-410) incorporated the NCI into NIH.
- October 18, 1971—President Nixon converted the Army's former biological warfare facilities at Fort Detrick, Maryland, to house research activities on the biology, causes, prevention, and treatment of cancer.
- December 23, 1971—The National Cancer Act of 1971 replaced the 1937 National Cancer Institute Act. It gave the NCI Bureau status, increased the authority and responsibilities of the NCI Director; required that the Director, NCI, and the Director, NIH, be appointed by the President; initiated a National Cancer Program; established the three-member President's cancer Panel to monitor the development and execution of the National Cancer Program; and restructured the National Advisory Cancer Council as a 23-member National Cancer Advisory Board responsible for advising the Director, NCI, regarding the activities of the National Cancer Program and approving cancer research grants.
- July 23, 1974—The National Cancer Act Amendments (P.L. 95-352) expanded the mandate of the NCI to include more emphasis

on research related to the prevention of cancer caused by occupational or environmental factors.

- November 9, 1978—The 1978 amendments to the National Cancer Act (P.L. 95-622) called for "... an intensified research program for the prevention of cancer caused by occupational or environmental exposure to carcinogens" and for programs to educate and train health professionals in the fundamental sciences and clinical disciplines related to cancer. The National Cancer Advisory Board's membership was increased from 23 to 29 members, 18 appointed by the President and 11 ex officio.

- 1980—The current Director of the Institute, Vincent T. DeVita, Jr., M.D., was appointed.

- 1985—This mandate was further emphasized by the Health Research Extension Act of 1985, P.L. 99-158, which required an Associate Director for Prevention in the Institute.

### Introduction

The general purpose of the NCI continues to be the conduct and support of research, training, health information dissemination, and related programs with respect to the cause, diagnosis, prevention, and treatment of cancer and the continuing care of cancer patients and the families of cancer patients.

To fulfill this mandate, NCI sponsors a broad range of research and research-related activities, both intramural and extramural, which include basic and applied research and a variety of professional and public education programs. In addition to conducting scientific investigations in its own laboratories and clinics, NCI provides grant and contract support for cancer research and cancer control programs at

institutions in the United States and abroad. The members of the National Cancer Advisory Board (NCAB) are presidential appointees, and the President's Cancer Panel is a three-member committee appointed by the President to advise him on the progress and activities of the National Cancer Program.

NCI research is carried out through a broad range of laboratory and clinical programs. In addition, NCI provides various research support services, including the development and distribution of critical materials such as viruses, drugs, equipment, and public and professional educational materials.

The research and research-related activities of the NCI are conducted by five Divisions in coordination with the Office of the Director. The functions of the Divisions and their major areas of responsibility are:

- *Division of Cancer Biology and Diagnosis (DCBD)*—Plans and directs research activities relating to basic cancer biology and diagnosis, monitors developments in these programs and assesses the national need for research, and fosters and guides an effective research program.

- *Division of Cancer Etiology (DCE)*—Plans and directs a national program of basic research that includes laboratory, field, and epidemiologic and biometric research on the cause and natural history of cancer and means for preventing it. DCE evaluates mechanisms of cancer induction and promotion by chemicals, viruses, and environmental agents including radiation; serves as the focal point for the Federal Government on the synthesis of clinical, epidemiological, and experimental data relating to cancer causation; and participates in the evaluation of, and advises the Institute Director on, program-related aspects of other basic research activities pertaining to cancer cause and prevention.

- *Division of Cancer Prevention and Control (DCPC)*—Plans and conducts basic and applied research and development, technology transfer demonstration, education,

and information dissemination programs to expedite the use of new information relevant to the prevention, detection, and diagnosis of cancer and pretreatment evaluation, treatment, rehabilitation, and continuing care of cancer patients throughout the country; plans, directs, and coordinates the support of research on cancer prevention and control at various institutions including cancer centers, community hospitals, and agencies of state and local governments, and through organ systems programs; coordinates a number of geographically based cancer reporting systems and applies statistical, analytic, and quantitative methods to monitor progress toward control in the United States; supports cancer research training, clinical education, continuing education, and career development in cancer prevention and control; administers programs for the support of construction, alteration, renovation, and equipping of extramural research facilities; and coordinates program activities with other Divisions, Institutes, or Federal and state agencies, establishing liaison with professional and voluntary health agencies, cancer centers, labor organizations, cancer organizations, and trade associations.

- *Division of Cancer Treatment (DCT)*—Plans, directs, and coordinates an integrated program of intramural and extramural preclinical and clinical cancer treatment research as well as research conducted in cooperation with other Federal agencies with the objective of curing or controlling cancer in humans by using various treatments alone or in combination; administers research and development programs in the areas of drug development, biological response modifiers, and radiation diagnosis and therapy development; and serves as the national focal point for information and data on experimental and clinical studies related to cancer treatment and for the distribution of such information to appropriate scientists and physicians.

- *Division of Extramural Activities (DEA)*—Plans and directs the conduct of key activities governing the review of grants and contracts for the Institute; provides staff support for the National Cancer Advisory Board and coordinates the Institute's review of research grants and training programs with the Board; provides reports and analyses of extramural activities to Institute staff; and takes the lead in formulating and coordinating the use of policies and procedures important to the conduct of extramural activities.

Each of the Divisions (except DEA) is advised by a Board of Scientific Counselors.

The recent advances and opportunities for future progress in biomedical research described in the remainder of this report represent highlights only and are intended to illustrate the scope and promise of the NCI's effort.

## Managerial Initiatives

Many scientific opportunities in cancer research were supported by four important managerial initiatives put in place this year.

### Supercomputer

During the last decade, there has been a biological revolution facilitated by major advances in technology including recombinant DNA technology, gene cloning, rapid DNA sequencing, and the use of monoclonal antibodies in the detection and treatment of disease. This has led to a body of data that, like the study of DNA previously, is almost impossible to fully analyze with present equipment. With the rapid advances in computer technology, however, the use of supercomputers in biology makes it possible to solve these extremely complex problems. Research topics that can be addressed by a powerful computer include sequence analyses of proteins and nucleic acids. Examples include determining the sequence of nucleic acid subunits that make up genetic structure, predicting the properties and structure of proteins from their amino acid sequence, and predicting protein folding patterns; study-

ing homologous relationships between regions of different nucleic acids and comparing them with existing data bases of genetic material sequences; graphically representing the structures of molecules; simulating molecular interactions; and x-ray crystallography studies. The speed of the supercomputer will greatly facilitate all these studies and enhance our understanding of molecular biology, an important part of NCI's programs.

The NCI supercomputer system became operational at the Frederick Cancer Research Facility in April 1986 and on the NIH campus within the Laboratory of Mathematical Biology, Division of Cancer Biology and Diagnosis. It is the first of its kind to be dedicated totally to biomedical research. It performs most calculations and procedures 50 to 100 times faster than alternative computing methods. The system includes powerful work stations having computational and graphic display capabilities, for example, drawings of proteins in three dimensions. A high-speed telecommunications network links researchers on the NIH Bethesda campus to the supercomputer and will tie into the Department of Health and Human Services (DHHS) telecommunications center to link other Department users to the supercomputer facility. While use of the supercomputer has begun with NCI research, the facility is being scaled up to support not only NIH and

DHHS scientific users, but also extramural scientists through grants in kind. The dedicated system gives scientists direct control over the supercomputer operations and applications so that the computer serves the scientists, rather than the other way around.

#### **NCI Partnership With State and Local Health Agencies**

The purpose of the Division of Cancer Prevention and Control's public health agency initiative is to increase the quantity and quality of cancer prevention and control programs conducted by state and local public health agencies and to promote the development of programs that will facilitate the achievement of NCI's year 2000 goals and objectives. Many state and local governments will fund cancer control activities but need advice on undertaking such efforts.

Begun a little over 2 years ago, this initiative includes: direct technical assistance to state and local public health agencies; preparation of guidelines and protocols for cancer prevention and control programs that can be adopted at the local level; information exchange covering the state of the science in cancer prevention and control and programs and legislation at the state and local levels; funding of demonstration projects for building the technical capabilities of health departments to conduct cancer prevention and control; and developing analytic

methods for using epidemiologic data to identify program priorities and resource needs at the state and local levels. The primary means of implementing this initiative include: direct staff interaction with agency personnel; developing and disseminating information on cancer control science and activities undertaken by others; funding of demonstration projects to evaluate methods of implementing cancer prevention and control intervention programs in public health agency settings; and coordinating activities to take advantage of existing knowledge and to avoid duplication of effort with other Federal agencies that interact with state and local public health departments. This program is being developed with the advice of a working group that includes a number of state, city and county health officers and cancer prevention and control program staff at the state level, as well as staff from the Centers for Disease Control (CDC). Coordination with the CDC avoids duplication of effort and makes maximum use of relevant expertise.

The response to this set of initiatives has been excellent. Public health agencies are clearly committed to chronic disease control issues. At the same time, it is evident there is need for technical assistance for models that demonstrate how to adapt and approach cancer prevention and control programs at the local level, rapid transfer of new scientific knowledge as it becomes available, and identifying and justifying the priority for support programs in cancer control that rely on local resources.

A measure of current interest in this program is the response from public health agencies to the NCI Request for Applications for developing technical capabilities leading to cancer prevention and control intervention programs at the state and local level. Twenty-nine applications were received, and 16 were approved. Four to six will be funded this year.



*NCI supercomputer at Frederick Cancer Research Facility showing workstations.*

### Physician Data Query

The NCI has initiated a number of programs to speed the transfer of new clinical research advances to practicing physicians. One such program, the Physician Data Query (PDQ), is a computer-based information system aimed at providing physicians with the latest information on cancer treatment. The PDQ system was designed by NCI, is updated monthly, and is available to physicians through the National Library of Medicine or from three commercial information system vendors. Two vendors are domestic; the third is European. It can be accessed on any home or office computer equipped with a modem. PDQ offers the most recent information on state-of-the-art and investigational cancer treatments, a listing of active cancer clinical trials, the patient eligibility requirements for entrance into those trials, and the names of associated investigators and contact persons. The system also contains lists of cancer specialists, primarily members of appropriate specialty societies. Each file is cross-referenced by cancer site, geographic area, and medical subspecialty. The availability of PDQ should result in improved access to state-of-the-art cancer care and, in conjunction with other NCI community programs, will provide improved cancer patient treatment and results.

NCI encourages both physicians and patients to be certain that state-of-the-art treatment is practiced, and that adequate drug doses are given in each case. It has been estimated that if every cancer patient in the United States were to receive the best treatment available today, there would be a 10 percent improvement in 5-year survival rates—a saving of 40,000 lives per year. PDQ serves as a convenient checkpoint for physicians. Patients can ask their physicians to use PDQ or can request information from the Cancer Information Service (toll-free 1-800-4-CANCER) to share with their physicians. Rapid implementation of the most effective treatments represents a major challenge to the NCI and the medical profession.

Proper delivery of existing effective therapies will lead to further improvements in cancer patient survival rates.

### Animal Facility Upgrading and Consolidation

The NCI continues to monitor, evaluate, and upgrade its intramural animal facilities and animal care and use practices to meet the American Association for Accreditation of Laboratory Animal Care (AAALAC) standards. Last year NCI restructured its Animal Research Committee to form an Institute-umbrella committee with representatives of each of the NCI intramural Divisions and the Office of the General Counsel. The Director, Laboratory of Animal Sciences, NCI, serves as the chairperson. This committee provides oversight for protocol review carried out by the Division subcommittees as well as animal facilities and use issues.

Recently NCI consolidated all animal support in central facilities in each of the NCI laboratory buildings on campus. The management responsibility and accountability for these facilities and associated resources are now centralized within the Laboratory of Animal Sciences, Office of the Director, NCI. This is a step forward in improving standards and methods of animal care and making more efficient and effective use of staff.

### Scientific Opportunities and Research Advances

#### Acquired Immune Deficiency Syndrome

##### *HTLV-III/LAV\**

The identification of HTLV-III as the etiologic agent for acquired immune deficiency syndrome (AIDS) was an important breakthrough because it created the possibility to develop an effective screening test and an effective vaccine for high-risk individuals. It has been found recently that HTLV-III has certain properties in common with HTLV-I, HTLV-II, and bovine leukemia virus. The similarity

\* The International Committee on the Taxonomy of Viruses recently proposed the name human immunodeficiency virus (HIV) for the AIDS retroviruses.

is seen in the way this group of viruses brings about the enhancement of its own growth (and eventually the death of host cells) through a transacting factor, probably a protein, which is coded for by the virus' own genome. HTLV-III is similar to several other retroviruses of domestic animals. These viruses are "slow" viruses (having a long latency period) belonging to the lentivirus subfamily and all affect cells of the immune system. Despite differences in the outcome of infection by various lentiviruses, there is an important point in common: once infected, individuals remain infected for life. Lentiviruses, like other retroviruses, integrate into the host's DNA and remain there as long as the cell is not killed, eliminated by the host immune system, or removed through senescence. Different strategies have evolved to avoid elimination of lentiviruses by the host's immune system. For some, apparently including HTLV-III, they do so by a process called "genetic drift" in which changes in the genes controlling the composition of their outer coating produce variants that escape immune detection, and the viruses are able to induce a new cycle of disease.

#### *Testing of Drugs*

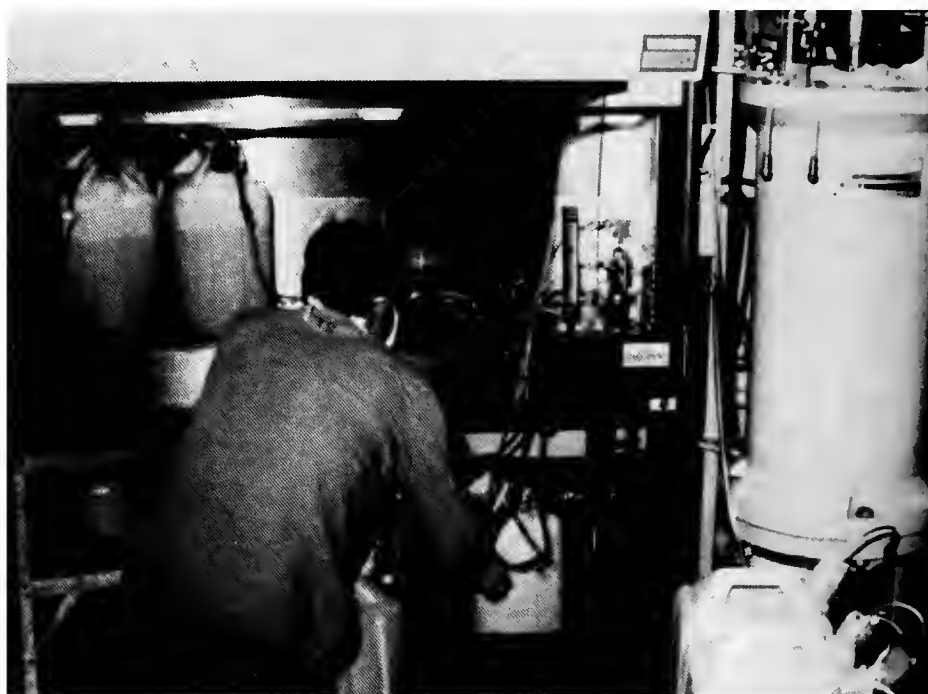
AIDS is almost always fatal and has attacked more than 21,000 Americans since 1981. The etiologic agent, HTLV-III, is a retrovirus transmissible by sexual contact and by blood and blood products. Some estimates indicate that as many as 1 million Americans and an undetermined number of people throughout the world may be infected with the virus. Although it is unclear what percentage of people who are currently infected with the virus will develop the disease, the 2-year mortality rate for reported cases of AIDS exceeded 80 percent in the United States in 1985.

Although the disease was first considered to be passed by male-to-male and male-to-female sexual contact, and blood product transmission, it has been documented that female-to-male sexual transmission may occur. It was recently shown

that a large number of prostitutes in many different countries are infected with the virus. These facts raise the possibility that exponential spread of HTLV-III within the heterosexual community may be imminent. The development of new treatments for AIDS is of vital importance in controlling the AIDS epidemic. A joint drug selection committee has been established by the NCI and the National Institute of Allergy and Infectious Diseases (NIAID) and agreement reached on the division and coordination of tasks. The NCI has agreed (in collaboration with NIAID) to assume primary responsibility for preclinical anti-AIDS drug development and for distributing the most promising agents to appropriate medical centers and physicians as efficacy is demonstrated. The NCI's capability to respond so readily to the urgency of the AIDS problem is due to the large science base previously developed through the Institute's prior support of virologic and immunologic basic research.

The selection of new agents for the treatment of AIDS has been expedited by the development of a high capacity drug screening system. The drug screen for anti-HTLV-III activity employs a clone (H9) of the OKT4+ T-cell (a cultured lymphocyte cell line) that is permissive to HTLV-III replication but partially resistant to its cytopathic effect.

The first compound that showed promise in the preclinical screen was suramin, which had been widely used in the past to treat two parasite infections—trypanosomiasis and onchocerciasis. *In vitro* studies confirmed that suramin inhibited the viral reproduction cycle through retroviral reverse transcriptase at drug levels which could be achieved in man. Suramin has since been proven to inhibit HTLV-III viral replication in patients and has now completed clinical phase II trials at several medical centers in the United States. No clinical improvement has been seen in these trials, and the agent has demonstrated toxicity. Suramin is currently considered to be inappropriate for single agent use in AIDS. A second



*AIDS laboratory at Frederick Research Cancer Facility.*

agent, 3'-azido-3'-deoxythymidine (AZT), was also highly active in the *in vitro* screen. Unlike suramin, which inhibits viral reverse transcriptase directly, 3'-azido-3'-deoxythymidine inhibits viral DNA elongation. Like suramin, azidothymidine inhibits HTLV-III replication in patients and has entered clinical phase II trials.

A family of 2',3'-dideoxy purine and pyrimidine analogs are now being tested, and preliminary results suggest that several of these hold unique promise as potential anti-retroviral agents because of their activity at extremely low drug levels. Two of the dideoxy compounds (dideoxycytidine and dideoxyadenosine) show special promise of efficacy and have entered the full preclinical development process.

The drug selection committee mentioned above is considering six agents for testing in the extramural AIDS treatment centers. They are Ribavirin, alpha-interferon, Foscarnet, HPA 23, dideoxycytidine, and azidothymidine. More information is needed on isoprinosine.

#### *AIDS Vaccine*

A number of different approaches to vaccine development are being simultaneously pursued since it is unknown which of them may be successful. It is extremely important that an animal model be developed for AIDS that can be used in the evaluation of treatment modalities and vaccines prior to testing in humans. Although the chimpanzee appears to be a useful model for monitoring a viral infection, it is expensive and in limited supply and is not a disease model because the chimpanzee never develops evidence of immunodeficiency even though it does develop a viral infection. In addition to pursuing this model, efforts to develop a less expensive and more practical animal model are under way.

#### **Viral Oncogenes as a Cause of Human Cancer (HTLV-I and -II, Papillomaviruses, EBV, and Hepatitis B)**

Extraordinary advances in knowledge and technology related to molecular biology made during the past few years have provided significant results regarding viruses as a cause of human cancer. The new technologies have made it



possible to identify in human cancer cells various specific oncogenes originally discovered in rodent and avian viruses. The normal cellular counterparts of about 30 of these genetic sequences, termed proto-oncogenes, appear in all human cells, and it is thought that they code for important cellular functions during differentiation. Their modification or activation may be responsible for the transformation of normal cells into malignant ones.

This possibility has served as an impetus to identify additional oncogenes, to understand the purpose for oncogenes in the normal cell, how they are activated, and to compare normal and abnormal oncogene products to determine when changes occur. Large amounts of cloned oncogene products can now be produced, and efforts are focused on determining their structure, active site, and biological activity. Strategies for preventing or treating cancer may depend on agents that interact with targets present only in cancer cells and essential to their proliferation. Oncogenes and their products may represent precisely such a target, and understanding oncogenes and the products they encode will enable researchers to devise methods to antagonize their function and to prevent cancer.

HTLV-I is now considered the direct causative agent for some human cancers, based on its strong epidemiologic association with T-cell leukemias and lymphomas. Studies of HTLV-I and the related virus, HTLV-II, are elucidating fundamental phenomena such as the mode of virus transmission, virus-host cell interactions, and the molecular basis of virus transformation.

Recent studies have suggested that the human papillomaviruses (HPV) have a pathogenic role in the development of certain human carcinomas, particularly those of the anogenital tract. In addition, these viruses have long been associated with many wart diseases. The DNA from HPV has been consistently detected in an unusual wart disease

known as epidermodysplasia verruciformis which frequently converts to carcinoma. It has been reported that HPV is present in several types of anogenital tumors such as cervical and vaginal carcinoma in situ and verrucous carcinoma. Another important observation which has further implicated HPV as the etiologic agent for cervical neoplasia was the detection of HPV DNA sequences in lymph nodes containing metastases. These lymph nodes were positive for the same HPV DNA sequences present in the primary cancer. This result clearly showed that HPV genes are associated with cancer cells and that the sequences are maintained in those cells for the several generations required to form a metastatic lesion. Thus the HPV genes appear to be necessary to maintain the malignant state.

#### *Role of Hepatitis B Virus and Liver Disease*

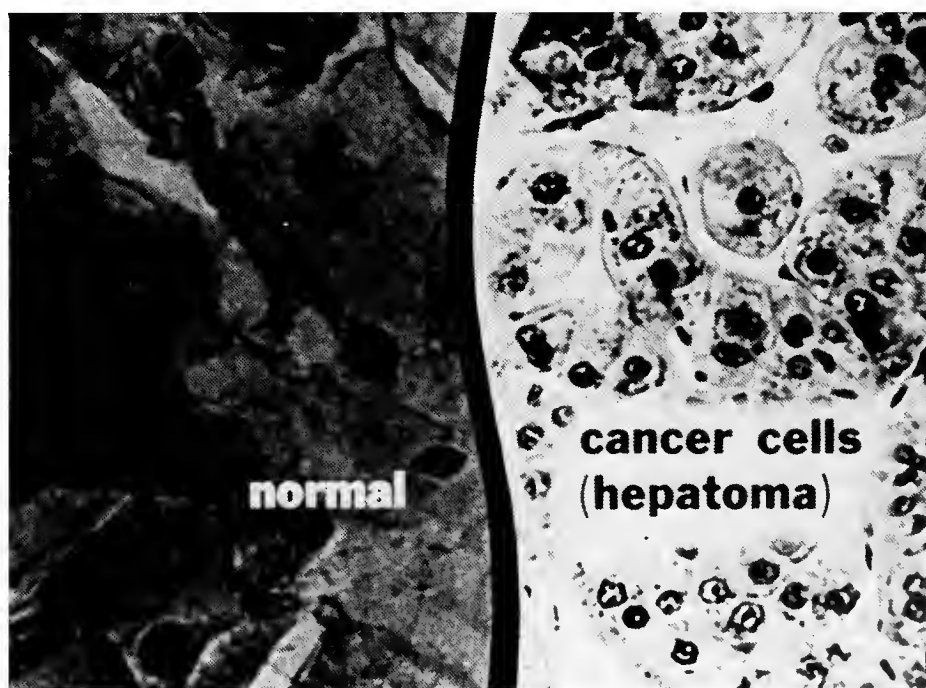
The strong association between chronic infection with hepatitis B virus and the subsequent development of primary hepatocellular carcinoma (PHC) is based exclusively on epidemiologic data. In spite of this association and that of the

virus with other diseases, little is known about the role of the virus in the pathogenesis of these diseases. Because of the medical importance of PHC in some regions, increased emphasis is being directed to the problem. The molecular mechanisms that underlie the interaction of the virus with liver cells in human and animal model systems, the relevance to human disease in model systems that are already developed, and the function of the gene products of the hepatitis B virus and whether any of them are transforming proteins are all being examined.

The hepatitis vaccine is being tested in developing countries where the disease is endemic not only as a preventer of hepatitis but also as primary prevention of PHC.

#### **Pleiotropic Drug Resistance**

One major obstacle to curing cancers with drugs has been the resistance cancer cells develop to the drugs. Recently, a new cell protein marker related to this phenomenon was discovered and found to be produced via gene amplification. The marker, called P170 glycoprotein, offers a target for a monoclonal antibody. An antibody to P170



*A comparison of normal versus hepatoma cells.*



may reverse the cancer cell's resistance to anticancer drugs thus enhancing their efficacy. Other research findings suggest that the basic process of cell transformation to cancer may at the same time amplify a cell's defenses against toxic substances so that it strongly resists foreign agents such as anticancer drugs. Increased levels of certain enzymes involved in natural defenses against toxins—protein kinase C and glutathione transferase—have recently been found in high levels in drug-resistant cells. The increased levels mimic those seen in the early stages of cancer transformation and offer, for the first time, a link between drug resistance and the fundamental cancer transformation process. This research also suggests new targets for cancer drug design, such as inhibitors of protein kinase C.

Whether the P170 proves to be the single explanation for pleiotropic drug resistance remains to be established. While it appears to be consistently present in a broad spectrum of resistant tumors derived in culture or in animals, certain features of drug resistance militate against the presence of a single protein change being responsible for the phenotype as multiple abnormalities have been found in selected cell types. In addition to the increase in P170 in a variety of drug-resistant cells and the finding of increased P20 in breast cancer cells, other protein changes have been found in drug-resistant cells of the pleiotropic phenotype.

NCI intramural scientists have identified a gene that is responsible for one type of multidrug resistance in cultured human cancer cells. A full length DNA copy (cDNA) of this multidrug resistant (MDR1) gene has been made and its DNA sequence determined. The cDNA provides a probe for measuring the expression of MDR1 in tumors and may help guide chemotherapy. The MDR1 gene product is the membrane glycoprotein described above. It binds to vincristine, verapamil, and related drugs and probably participates in drug transport out of cells.

### **Adoptive Immunotherapy: Improved Methods and Clinical Trials**

This year a very exciting clinical trial with a new biological was reported using what is called adoptive immunotherapy. This involves activating anticancer immune cells taken from the cancer patient and then returning them. The patient's white blood cells (lymphocytes) are removed and then exposed in culture to high concentrations of T-cell lymphokine growth factor or interleukin 2 (IL-2), discovered earlier by a researcher at NCI. This generates lymphokine-activated killer (LAK) cells which are then transfused back into the patient along with doses of systemic IL-2. Results in patients with advanced cancer have been most promising. As of April 25, 1986, of 55 evaluable patients, 21 had objective responses, and of these, five were in complete regression. A small confirmatory trial is currently under way at the Frederick Cancer Research Facility.

NCI is currently funding extramural trials in six medical centers to confirm the findings. Since LAK/IL-2 therapy presently appears most effective against melanoma, colon, and kidney cancers, patients with advanced stages of these cancers are eligible for the trials at the centers. At a later time it is hoped to identify other sensitive tumors.

Approximately 50 patients for whom other therapies have failed will be treated at each of the following locations: New England Medical Center, Montefiore Medical Center/Albert Einstein College of Medicine, Loyola University Medical Center, University of Texas Health Science Center at San Antonio/Audie Murphy Veterans Administration Hospital, Cancer Research Institute of the Medical Center at the University of California, San Francisco, and the City of Hope National Medical Center.

Because the limiting factor in these trials is the generation of LAK cells, an automated technique is currently under development. Efforts are also directed toward

abrogating the toxicity of IL-2, and additional studies include combination therapy with drugs and radiation and alternative methods of administration.

### **Adjuvant Chemotherapy**

It has been learned from the treatment of breast cancer that therapy of advanced disease that produced responses could lead to prolonged survival if combined with primary surgical resection. One explanation for this is that microscopic disease is more easily eradicated than is bulky metastatic tumor. This hypothesis is being pursued in breast cancer and a variety of other cancers.

#### *Breast Cancer*

In September 1985, mortality data for breast cancer patients in chemotherapy and hormonal treatment clinical trials worldwide were carefully analyzed by experts led by Richard Peto of Oxford, and new guidelines for treatment were drawn up at an NIH Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer.

The analysis of mortality data indicated, for example, that adjuvant treatment of breast cancer patients under age 50 with chemotherapy could avoid about 25 percent of early deaths; that is, deaths within the first 5 years related to the breast cancer in this group. The analysis also indicated that when women over 50 whose cancer cells were estrogen-receptor positive received tamoxifen as adjuvant therapy, about 20 percent of early deaths were avoided. With this in mind, the consensus development panel concluded that: "Adjuvant chemotherapy and hormonal therapy are effective treatments for breast cancer patients. While significant advances have been made in the past 5 years, optimal therapy has not been defined for any subset of patients. For this reason, all patients and their physicians are strongly encouraged to participate in controlled clinical trials."

### *Renal Adenocarcinoma*

Up to 75 percent of patients with tumors that appear completely resected later develop metastatic tumor, presumably because microscopic metastases remained after surgery. Preliminary results using IL-2 and LAK cell therapy in advanced renal cancer have shown marked reductions of large tumor masses in all 11 patients treated, a significant new accomplishment in this disease. This is an important opportunity to explore the use of adjuvant therapy with IL-2 and LAK cells following nephrectomy (surgical removal of a kidney).

### *Colorectal Cancer*

Many colorectal cancer patients have unrecognized residual disease following surgery which ultimately results in death. Postoperative radiation therapy has been of value in rectal cancer but few options exist for patients with colon cancer. The addition of the immune system stimulant levamisole to chemotherapy with 5-fluorouracil has been found to reduce significantly the incidence of postoperative recurrent disease and result in longer survival. This form of chemotherapy will be combined with radiotherapy for colon and rectal cancer patients.

### *Lung Cancer*

Most lung cancer patients having apparently resectable disease ultimately succumb to recurrent tumor. Combination chemotherapy has produced significant, but temporary, tumor shrinkage in up to 40 percent of patients with advanced disease. This response to treatment and the longer survival that it provides occurred more frequently in patients not yet debilitated from their cancer. Such therapy may be particularly valuable for patients who have just recovered from their surgery, at the time when any remaining cancer is quite small. In a 130-patient study comparing chemotherapy to immunotherapy (levamisole and BCG) in patients who had all apparent tumor completely resected, cancer did not recur as quickly in the chemotherapy-treated patients, and survival was longer.

Another promising role for drug and/or radiation treatment in lung

cancer involves patients whose tumors have not metastasized but are considered too large for surgical removal. The use of drug combinations such as 5-fluorouracil and cisplatin, before radiation, can shrink these previously unresectable tumors to a size that can permit surgery. This approach opens the door to potentially curative therapy for patients whose prognosis has been poor.

The autocrine cancer hypothesis suggests that one way in which cells may become transformed is by producing their own growth factors for which they have receptors and to which they can respond. It has been found that high levels of bombesin (a gastrin-releasing peptide) are produced by human small cell lung cancer cells. Monoclonal antibodies to bombesin have been found to inhibit the autocrine stimulation of growth caused by bombesin and thus to inhibit lung cancer growth.

The monoclonal antibody is currently being made in preparation for antibombesin clinical trials in small cell lung cancer which are expected to begin in the near future.

### *Head and Neck Cancer*

Preliminary results using radiation and chemotherapy before and/or after surgery have been dramatic. A major national effort is ongoing to treat more patients with this disease with the combined modalities in the hope that their prognoses can be substantially improved.

### *Cancer Metastasis*

Invasion and metastasis is the major cause of treatment failure for patients harboring malignant tumors. Over the past year significant progress has been made in understanding the biochemical and genetic mechanisms involved in this complex process.

### *Cloning the Gene for the Human Laminin Receptor*

During the process of metastases, tumor cells escape from the primary tumor and enter the blood stream. The circulating tumor cells attach to the wall of the blood vessel and penetrate the wall to enter the adja-

cent normal tissue where they initiate a new growth. The tumor cells use a special binding protein called the laminin receptor to attach to the blood vessel wall. Scientists have now cloned the gene for the human breast cancer laminin receptor. This has led to the discovery of a new class of experimental therapeutic agents that block this receptor and inhibit metastases in animal experiments. Clinical trials are planned to begin after FDA approval of the agents.

### *Discovery of the Autocrine Motility Factor*

One of the least understood properties of the malignant process is tumor invasion, the process by which tumor cells infiltrate normal tissue adjacent to the tumor mass. Scientists have discovered a new tumor protein that plays an important role in invasion by stimulating the migration or "crawling" of the tumor cells. This protein is markedly elevated (100-fold) in certain highly aggressive tumor cells compared to their noninvasive counterparts. Blocking of this protein could serve as a new approach in cancer therapy.

### *Discovery of Genes that Regulate the Metastatic Process*

Oncogenes are a family of altered normal genes that cause uncontrolled cell growth and may play a major role in the development of malignant tumors. Scientists have now found that one of these oncogenes (called "ras"), but not the others, causes cells to become highly metastatic. In order to cause metastases, the ras oncogene must interact with other specific cellular genes. This provides the first genetic approach to studying the factors necessary for metastatic behavior. Scientists have also discovered a gene associated with inhibition of metastases. This information may lead to new strategies for cancer therapy by blocking the genes that cause metastases or stimulating the genes that inhibit metastases.

## Development and Implementation of Mechanistically Oriented Antitumor Drug Prescreens

Recent advances in basic cancer research have made possible the identification of increasing numbers of targets for antitumor drug development. In the case of small cell lung cancer, an example is the autocrine growth factor bombesin. Other examples include oncogenes and their expression in malignant cell populations, the various steps in the metastatic process such as laminin/receptor interactions, secretion of type IV collagenase, etc. Identification of such targets makes feasible the development of specific mechanistically oriented antitumor drug prescreens. Such prescreens could be of great value when used in conjunction with the *in vitro* disease-oriented cell line screening project currently under development. This latter project has been planned as a primary drug screening model with an annual testing capacity of 10,000 to 20,000 compounds. The potential of this primary screen for detecting of compounds with selective cytotoxicity for particular tumor types could be significantly increased if relevant mechanistically oriented biochemical prescreens were employed. Examples of such prescreens are tests for agonists/antagonists of bombesin/receptor interactions as for EGF receptor, and for inhibitors of protein kinase C. Compounds shown to be specific inhibitors of such processes (prescreen actives) could then be screened in the disease-oriented cell line panels with special emphasis on specific cancer types (e.g., bombesin-directed actives tested against small cell lung cancer). Use of sensitive cell-free prescreens would permit testing of very large numbers of compounds and focus the cell line screen on compounds having biological activity in the tumor types of interest.

Appropriate molecular targets for development of prescreens are being identified through workshops involving recognized experts and NCI staff.

In addition to determining the relevance and potential for exploiting various molecular targets, the feasibility of developing high capacity assays will be considered.

In order to exploit multiple targets with this prescreening strategy, about ten prescreening systems will be operated simultaneously, and new prescreens will be added as technology and testing capacity permit. Each of the ten prescreening models used each year has a testing capacity of 10,000 compounds for a total annual capacity of 100,000 samples.

## The Biennial Report of the Director, National Heart, Lung, and Blood Institute

### History

The following events represent milestones in the development of the National Heart, Lung, and Blood Institute (NHLBI).

- June 16, 1948—President Truman signed the National Heart Act (P.L. 80-655), creating and establishing the National Heart Institute (NHI) in PHS and the National Advisory Heart Council.

- August 1, 1948—The Surgeon General, by General Circular 36, Organization Order No. 14, established NHI as one of the National Institutes of Health to administer functions of heart research, training, and administration set forth in the National Heart Act. Intramural research projects in cardiovascular diseases and gerontology conducted elsewhere in NIH were transferred to NHI.

- September 8, 1948—The first meeting of the National Advisory Heart Council was held.

- July 1, 1949—A comprehensive plan for NHI's intramural research program was instituted, organized on three general research levels, with three laboratory sections, five laboratory-clinical sections, and four clinical sections. The Heart Disease Epidemiology Study at Framingham, Massachusetts, was transferred from the Bureau of State Services, PHS, to NHI.

- January 18, 1950—The first National Conference on Cardiovascular Diseases, sponsored by NHI and the American Heart Association, was held in Washington, D.C.

- July 6, 1953—The first patient for heart disease research was admitted to the Clinical Center.

- February 19, 1959—A report to the Nation was presented by the American Heart Association and NHI: *A Decade of Progress Against Cardiovascular Disease*.

- April 21, 1961—The President's Conference on Heart Disease and Cancer, whose participants on March 15 were requested by President Kennedy to assist "in charting the Government's further role in a national attack" on these diseases, convened at the White House and submitted its report.

- November 22, 1964—The Second National Conference on Cardiovascular Diseases was held under the cosponsorship of the American Heart Association, NHLI, and the Heart Disease Control Program of PHS, to appraise developments since the first conference in 1950 and to determine needs and opportunities for continued and accelerated progress against heart and blood vessel diseases.

- December 9, 1964—The President's Commission on Heart Diseases, Cancer and Stroke, which was appointed to "recommend steps that can be taken to reduce the burden and incidence of these diseases," submitted its report.

- October 16, 1968—A Nobel Prize in Medicine was awarded to Dr. Marshall W. Nirenberg, Chief of NHLI's Laboratory of Biochemical Genetics, for discovering the key to deciphering the genetic code. He was the first Nobel Laureate at the NIH and the first Federal employee to receive a Nobel Prize.

- November 10, 1969—The National Heart Institute was renamed the National Heart and Lung Institute, reflecting expansion of its functions.

- February 18, 1971—In his Health Message to the Congress, the President identified sickle cell anemia as a high-priority disease target and called for increased Federal expenditures. Subsequently, the DHEW Assistant Secretary for Health and Scientific Affairs assigned the lead-agency responsibility for coordinating a National Sickle Cell Disease Program to NIH and NHLI.

- June 12, 1972—The HEW Secretary approved a nationwide program of hypertension information and education. He appointed the Hypertension Information and Education Advisory Committee, chaired by the Director, NIH, and

the Interagency Working Group, chaired by the Director, NHLI, to implement the national effort. A High Blood Pressure Information Center was established within the NHLI Office of Information to collect and disseminate public and professional information about this disease.

- July 14, 1972—The HEW Secretary approved a reorganization of NHLI, elevating the Institute to Bureau status within NIH, with seven division-level components: Office of the Director, Division of Heart and Vascular Diseases, Division of Lung Diseases, Division of Blood Diseases and Resources, Division of Intramural Research, Division of Technological Applications, and Division of Extramural Affairs.

- July 24, 1973—The 5-volume *National Heart, Blood Vessel, Lung, and Blood Program* report was transmitted to Congress. The comprehensive 5-year plan of attack against heart, blood vessel, lung, and blood diseases and research and management of blood resources was developed by the Director, NHLI, with the advice of the National Heart and Lung Advisory Council, in accordance with a provision of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423).

- August 2, 1974—Regulations were approved governing the establishment, support, and operation of National Research and Demonstration Centers for heart, blood vessel, lung, and blood diseases. The regulations concerned the implementation of section 415(b) of the PHS Act, as amended by the National Heart, Blood Vessel, Lung, and Blood Act of 1972, which authorized the establishment and support of National Research and Demonstration Centers.

- June 25, 1976—NHLI was redesignated the National Heart, Lung, and Blood Institute by the Health Research and Health Services Amendments of 1976 (P.L. 94-278). The 1976 act further enlarged Institute authority to advance the national attack on heart, blood vessel, lung, and blood diseases

and the conduct of research in the use of blood and blood products and in the management of blood resources.

- August 1, 1977—The Biomedical Research Extension Act of 1977 (P.L. 95-83) reauthorized the programs of the National Heart, Lung, and Blood Institute, with continued emphasis on both the national program and related prevention and dissemination activities.

- December 17, 1980—The Health Programs Extension Act of 1980 (P.L. 96-538) reauthorized the National Heart, Lung, and Blood Institute with continued emphasis on both the national program and related prevention programs.

- September 8, 1981—The Working Group on Arteriosclerosis, convened in 1978 to assess present understanding, highlight unresolved problems, and emphasize opportunities for future research in arteriosclerosis, completed its report. Volume I of the report presented conclusions and recommendations in nontechnical language. Volume II provided in-depth, substantial bases for the conclusions and recommendations contained in Volume I.

- 1982—Dr. Claude Lenfant was appointed Director of the Institute.

## Introduction

The National Heart, Blood Vessel, Lung and Blood Act of 1972 (P.L. 94-423), which enlarged the authority of the NHLI, provided for expanded, intensified, and coordinated institute activities in accordance with a comprehensive National Heart, Blood Vessel, Lung, and Blood Diseases Program. Four years later, the NHLI was redesignated the National Heart, Lung, and Blood Institute (P.L. 92-423), and its mandate was further expanded to include research on the use of blood and blood products and the management of blood resources.

Institute responsibilities outlined in the Law include:

- Research on the epidemiology, etiology, and prevention of heart, blood vessel, lung, and blood diseases.

- Research on basic cardiovascular, lung, and blood biological processes.

- Research on heart, blood vessel, lung, and blood diseases of children.

- Development and evaluation of techniques, drugs, and devices to aid diagnosis and treatment.

- Programs to develop devices to assist, replace, or monitor vital organs.

- Field studies and large-scale tests relating to heart, blood vessel, lung, and blood diseases.

- Research on the uses of blood and blood resources in the United States, including such items as collection, preservation, fractionation, and distribution.

- Education and training of scientists and medical investigators.

- Public and professional education programs in all aspects of these diseases.

- Programs for research and development of emergency medical services, including training of paraprofessionals and development of specialized equipment and communications.

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood and in the uses of blood and the management of blood resources. It plans, fosters, and supports, through research in its own laboratories and through extramural research grants and contracts, an integrated and coordinated program that includes basic investigations, clinical trials, and demonstration and education projects relating to the causes, diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases. The Institute supports research training and career development in basic and clinical research relating to these topics.

Diseases within the mandate of the Institute have a major impact on the American people. Together, all cardiovascular, lung, and blood diseases accounted for 1,142,000

deaths in 1984 and 56 percent of the total economic cost of illness and premature death.<sup>1,2</sup>

Cardiovascular, lung, and blood diseases account for 5 of the 10 leading causes of all deaths, 5 of the 10 leading causes of infant deaths, and 5 of the 10 leading chronic conditions causing limitation of activity.<sup>1,3</sup> Cardiovascular diseases caused nearly one of every two deaths in 1984. Lung diseases, even after excluding lung cancer, caused an estimated 174,000 deaths in 1984. Blood-related disorders such as Cooley's anemia and sickle cell disease are either fatal themselves or are a frequent contributing factor in the development of diseases that are fatal.

Over the past 20 years, there have been significant declines in mortality for the cardiovascular diseases, but an increase in mortality from chronic obstructive pulmonary disease. The overall improvement in mortality from cardiovascular diseases is reflected in the rapid increase in life expectancy in recent years. The age-adjusted rate for all causes of death dropped from 739 deaths per 100,000 in 1964 to 547 per 100,000 in 1984, with 70 percent of this reduction attributable to the decline in the death rate for cardiovascular diseases.

The NHLBI coordinates its research programs and other activities with all relevant components of the NIH and with other Federal programs with responsibilities related to cardiovascular biomedical engineering; blood resources and blood substitutes; smoking and heart, lung, and blood diseases; lipid and lipoprotein comparability; and the costs and benefits of health research. The coordination is accomplished through the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources (P.L. 99-158).

(1) *Vital statistics of the U.S., National Center for Health Statistics.*

(2) *Estimated by NHLBI based on morbidity, mortality, and cost data from the National Center for Health Statistics and health expenditures estimated by the Health Care Financing Administration.*

(3) *National Health Interview Survey, 1980, National Center for Health Statistics.*

The Institute sponsors educational programs for health professionals and the lay public, such as the National High Blood Pressure Education Program and the National Cholesterol Education Program. It also develops relationships and collaborates with various types of institutions; professional associations; international, national, and state agencies; business and labor organizations; and voluntary community and civic health groups. The activities include the development of risk factor reduction programs and dissemination of messages and materials on the diseases within the Institute's purview, with emphasis on prevention.

The NHLBI uses traditional mechanisms such as pre- and postdoctoral fellowship awards and research training grants to ensure an adequate base of research personnel skilled in scientific areas relevant to the Institute's mandate. In addition, the Institute develops new research training and career development programs to meet certain specialized personnel needs. The NHLBI research training and career development programs include:

- The National Research Service Award for individual postdoctoral fellows.

- The National Research Service Award for institutional research training.

- The Minority Access to Research Careers Program.

- The Minority Biomedical Research Support Program.

- The Minority School Faculty Development Award.

- The Minority Institutional Research Training Program.

- The Minority Summer Program in Pulmonary Research.

- The Preventive Cardiology Academic Award.

- The Transfusion Medicine Academic Award.

- The Clinical Investigator Award.

- The Physician Scientist Award.

- The Research Career Development Award.

## Heart and Vascular Diseases Program

The focus of the heart and blood vessel disease program is on increasing the knowledge of causes, diagnosis, treatment, and prevention of these diseases. Research support is divided among 10 program areas: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart disease, cardiomyopathies and infections of the heart, and circulatory assistance. Advances in knowledge about the basic biological processes and the mechanisms of normal and abnormal heart and blood vessel phenomena are applied to the prevention and treatment of disease.

### Major Research Progress

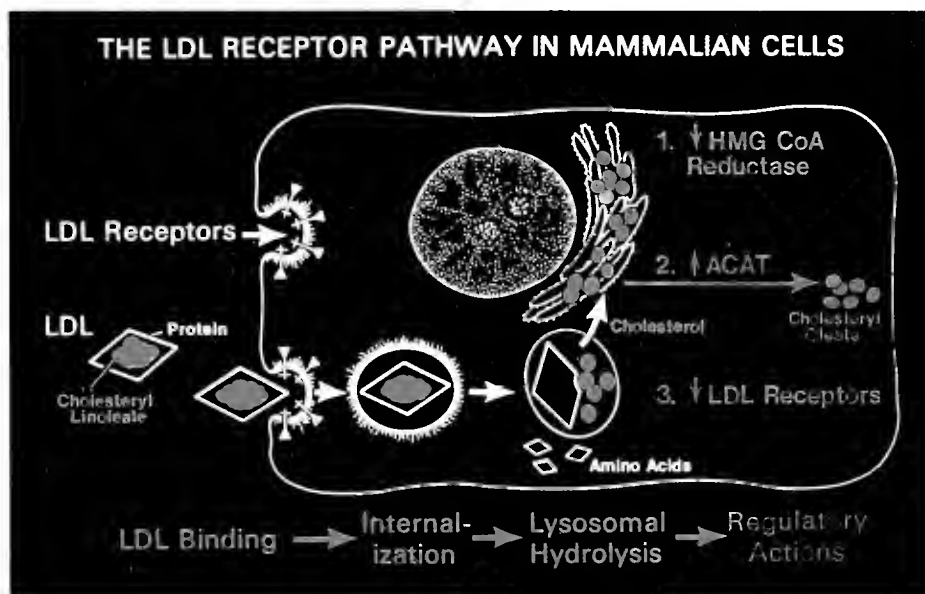
Highlights of major research advances in the heart and vascular diseases program are provided below.

#### *The Low Density*

#### *Lipoprotein Receptor*

Familial hypercholesterolemia is an hereditary disease that in its heterozygous form afflicts about one in 500 persons throughout the world. Individuals with this form of the disease have elevated levels of low density lipoprotein (LDL) and cholesterol, a substance carried by the LDL. Those with homozygous familial hypercholesterolemia (about one in 1,000,000 persons) have extremely high LDL levels and high total cholesterol levels and usually develop coronary heart disease in their teens or even earlier.

In studying patients with familial hypercholesterolemia, investigators discovered that in this rare subgroup of homozygotes, LDL receptors were either nonfunctional or severely defective. The discovery of this receptor and of its presence in many body cells, particularly in the cells of liver, has revolutionized the understanding of cholesterol and lipoprotein metabolism. Each step in the cellular processing of cholesterol has been meticulously defined. In a process called receptor-mediated endocytosis,



*Schematic of the sequential steps in the LDL receptor pathway of mammalian cells. Receptor-mediated endocytosis of LDL is also illustrated.*

which plays a fundamental role in the growth, nutrition, and differentiation of all mammalian cells, the LDL is taken into the cells and broken down where it yields its cholesterol to serve the cells' needs.

Some persons with familial hypercholesterolemia can now be treated and their cholesterol levels reduced by certain drugs either already in existence or under development. In addition, the discovery of the mechanism of the intracellular LDL pathway provides a model for study of the action of the more than 20 receptors that are involved in receptor-mediator endocytosis, and it opens a way for analysis of genetic diseases caused by defects affecting other receptors. For their pioneering work, Drs. Brown and Goldstein were awarded the 1985 Nobel prize in medicine and physiology.

#### *Atrial Natriuretic Hormone and the Control of Blood Pressure*

Research during the past few years has resulted in the isolation, purification, and characterization of a peptide hormone called atrial natriuretic hormone that is capable of lowering blood pressure. The hormone is derived from granules in atrial muscle cells, and it appears to link the heart, kidneys, adrenals, blood vessels, and brain in a

homeostatic control system that regulates blood volume and blood pressure.

The hormone is normally found at low levels in the circulation and is continuously released. Increases in plasma levels have been shown to be produced by the stretching of the atrial muscle following blood volume expansion, by vasoconstrictors that produce hypertension, by high dietary salt intake, and by similar circumstances where there is a need perceived by the receptor to reverse rising blood pressure or expanding blood volume.

The characterization of the hormone and the likely availability in the near future of long-lived active analogues promise a new pharma-



*Section of a normal atrial cardiocyte showing secretory granules.*



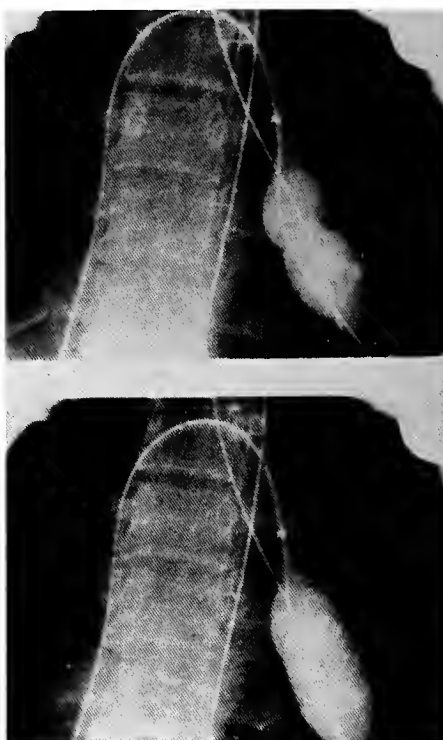
ceutical approach to the treatment of hypertension particularly in patients for whom conventional diuretic therapy is ineffective or results in undesirable side effects, and of diseases of the liver and kidney.

#### *Injury Caused by Free Radicals During Reperfusion of Ischemic Tissue*

Reperfusion of ischemic tissue results in the sudden production of oxygen-free radicals, which may be responsible for producing cellular injury. Research efforts focus on direct measurement of the production of free radicals, identification of the mechanism(s) for their production and elimination, and evaluation of pharmacological agents which, when administered during reperfusion, may prove clinically useful to decrease the production or enhance the breakdown of free radicals. In animal studies, investigators now utilize the technique of electron paramagnetic resonance spectroscopy to measure directly the production of free radicals. The oxygen-free radicals are found to be markedly increased during the initial period of reperfusion. Efforts to identify pharmacological agents that may enhance the removal of free radicals are directed toward the administration of superoxide dismutase (SOD) at the moment of reperfusion. Superoxide dismutase has already been administered to minimize oxygen toxicity in the lungs of premature infants and to reduce inflammation in a variety of arthritic conditions. Animal studies have demonstrated that recombinant human SOD improves postischemic myocardial function and metabolism by decreasing the amount of oxygen-free radicals present during reperfusion. Conceptually, SOD may be useful clinically in the treatment of acute myocardial infarction by reducing reperfusion injury following thrombolysis. Clinical studies are planned to test the efficacy of SOD.

#### *Percutaneous Balloon Catheter Valvuloplasty and Rheumatic Heart Disease*

Although rheumatic heart disease has decreased significantly in



*Upper: Balloon inflation at the beginning of valvuloplasty. Lower: Balloon inflation at the conclusion of valvuloplasty.*

developed countries, it remains the most common cardiac disorder in much of the world. Of the cardiac malfunctions that can result from rheumatic disease, mitral stenosis is perhaps the most common. Several surgical options are available for the management of established rheumatic mitral stenosis.

The recent development of percutaneous transluminal angioplasty has led to the development of that technique for opening up the narrowed mitral valve without surgery. This technique involves a large balloon at the tip of the special catheter that is introduced through a vein in the leg, advanced to the heart and through the atrial septum, positioned in the mitral valve and then briefly distended under high pressure to force the mitral valve further open. One group of investigators undertook balloon dilation of the heart valves of eight young patients with rheumatic heart disease, ranging in age from 9 to 23 years, with prompt relief of symptoms. Followup catheterization demonstrated continued

hemodynamic improvement, with evidence of partial restenosis in only one patient. Although these short-term results are favorable, longer-term followup studies are needed to fully assess this technique.

#### *New Information About Ischemia in Patients with Atypical Angina*

In a clinical study a few years ago, about two-thirds of a group of patients with angina-like pains but with normal large coronary arteries showed, in response to pacing-induced stress, inadequate increases in coronary blood flow and decreases in coronary resistance. The investigators concluded that the patients' small coronary arteries had a reduced capacity to vasodilate in response to increases in myocardial oxygen demand, which could lead to myocardial ischemia. Furthermore, drugs or endogenous substances with vasoconstrictor potential could further compromise vasodilation. The hypothesis that the study patients experienced myocardial ischemia was confirmed by decreased myocardial lactate consumption, increased left ventricular end-diastolic pressure, and abnormalities in left ventricular contraction during pacing.

In a subsequent study, investigators administered the potent coronary arteriolar vasodilator, dipyridamole, to determine whether the reduced vasodilation occurred only in response to metabolic stimuli, such as pacing-induced increases in myocardial oxygen demand, or resulted from a diminished capacity of the coronary vessels to dilate. Patients with impaired vasodilator reserve in response to increased myocardial oxygen demands exhibited an abnormally low response to dipyridamole. This finding suggests that the maximum vasodilator capacity of the coronary vessels was reduced. The study results are consistent with the hypothesis that some patients with angina-like pains and with small coronary arteries that angiographically appear normal, exhibit abnormalities in the maximum vasodilator capacity of the vessels.



### *A Possible New Approach to Alleviating Ischemia*

Angiogenesis is the process by which new capillaries are formed. It occurs normally during embryonic development and during ovulation and wound healing in later life, but it is also involved in several pathological conditions. Over a decade ago, cancer researchers suggested that increases in certain solid tumor cell populations were preceded by an increase in new capillaries, which converge on the tumor and supply it with blood. Subsequent investigations were focused on the development of inhibitors of angiogenesis. A few years ago, cardiology researchers recognized that these developments may be relevant to the improvement of blood flow to the heart muscle of patients whose coronary arteries were extensively diseased and narrowed by severe atherosclerosis but could not be bypassed surgically. Scientists are studying the therapeutic value of heparin, heparin fragments, and endothelial cell growth factors in these patients to induce blood vessel growth and capillary formation.

### *Relation of Serum Lipoprotein Levels to Early Atherosclerosis*

A form of atherosclerotic lesion is fibrous plaque, which consists of increased intimal smooth muscle cells in combination with a connective tissue matrix and variable amounts of intracellular and extracellular fat. The fatty streak, a possible precursor of the plaque, is a lipid-rich lesion commonly found in the arteries of children.

The Bogalusa Heart Study is a long-term community-based epidemiologic assessment of cardiovascular risk factors in young individuals (birth to age 26) in a biracial population. Four cross-sectional surveys of the study population have been conducted and risk factor data have been correlated with postmortem findings as they became available. In this young group, 88 deaths have occurred among persons between the ages of 3 and 26 years. Postmortem examinations showed extensive involvement of the intimal surface of

the aorta with fatty streaks, with blacks showing approximately twice as much involvement as whites. Small fatty streaks were seen in the coronary arteries of both races. The aortic fatty streaks were strongly related to ante mortem levels of both total cholesterol and low density lipoprotein cholesterol independently of race, sex, and age, and were inversely correlated with the ratio of high density lipoprotein cholesterol to the sum of the LDL cholesterol and very low density lipoprotein cholesterol. These findings show the strong relationship between plasma cholesterol levels and the development of atherosclerotic lesions in childhood and adolescence similar to the already established relationship in adults. They also suggest that atherosclerosis is initiated in childhood, and strengthen the view that measures to prevent atherosclerosis should be initiated in childhood.

### *Clarification of Type A Personality and Coronary Heart Disease Risk*

Medical literature has suggested that individuals characterized as having the type A behavior pattern (competitive, hostile, impatient, time urgent) are at higher risk for coronary heart disease (CHD), but

recent studies have not produced conclusive findings. The presence of the type A behavior pattern is a significant predictor of CHD events among adults who were not initially selected for CHD risk. The data remain equivocal among postinfarction patients. These findings have stimulated efforts to move beyond the general type A concept and define the contribution of specific components of type A to the relationship between CHD and behavior. Extensive behavioral evaluation of over 2000 patients who have had coronary angiography showed a strong age-related effect of type A on coronary artery disease risk. The predicted relationship between type A and CHD severity holds true for younger patients, but disappears and even tends to reverse in those over age 55. This interaction may explain the failure of some previous studies to find a relationship. More important, substantial evidence from this sample suggests that hostility, anger, and cynicism are the most important components of the global type A concept and are significantly related to CHD incidence and CHD mortality. Because these elements are also considered to be important



*Coronary arteries from a 23-year-old white male who died of multiple injuries from an automobile accident. The dark area shows surface involved with atherosclerosis.*

parts of the normal personality, research is continuing with the objective of determining the mechanisms by which components of the type A behavior pattern might influence the development of cardiovascular disease.

*High Density Lipoprotein Cholesterol, Coronary Heart Disease, and the Framingham Study*

A previous report from the Framingham Heart Study, based on 4 years of followup, demonstrated an inverse relationship between high density lipoprotein (HDL) cholesterol and coronary heart disease incidence. A recent study has extended followup observations to a period of 12 years. Data analysis in the study was confined to the 2,033 people for whom complete risk factor information was available. The Framingham followup is the only study that simultaneously considers lipoprotein cholesterol levels, cigarette smoking, blood pressure, relative weight, and alcohol ingestion as they relate to the incidence of CHD in subjects who have survived and not developed cardiovascular disease during middle age. Major new information pertains to alcohol consumption and cigarette smoking as additional independent variables that relate HDL cholesterol to subsequent CHD incidence. The study suggests a relationship between HDL cholesterol levels and 4-year incidence of CHD when both alcohol and cigarette smoking are "controlled" in the multivariate model. The well-documented negative influence of cigarette smoking and the positive influence of alcohol intake on HDL cholesterol suggests that these factors must be considered as potential confounders of the HDL cholesterol-CHD relationship. In addition, measurements of fasting HDL cholesterol are highly correlated with those from nonfasting specimens, and nonfasting values are as useful as fasting values for the estimation of CHD risk. The association was equally strong at all ages for the three-decade groupings above age 60.

*Success of the Statewide Coordination Program for High Blood Pressure Control*

The Statewide Coordination Program for High Blood Pressure Control, congressionally mandated in 1976, called for coordination of education and screening resources, for referral and treatment guidelines, and for promotion and sharing of effective methods for high blood pressure control among the communities within each state. The states in the program were California, Connecticut, Georgia, Maine, Maryland, Michigan, and South Carolina. On the basis of survey data from all seven states and without reference to population increases, it can now be conservatively estimated that by the end of 2 1/2 to 3 years of coordinated educational and intervention efforts, over 500,000 more hypertensives in participating states are now taking antihypertensive medication and more than 290,000 additional hypertensives are controlled below 140/90 mm Hg than at the start of the program.

**Research Needs**

*Blood Interactions with Natural and Synthetic Surfaces*

Over two million invasive cardiovascular procedures are performed annually in the United States. These include implantation of vascular grafts, heart valves, indwelling canulae, catheters, fistulas, major arterial reconstructions, ventricular assist devices, and artificial hearts. Materials from which these devices are made include synthetic fabrics, polymers, metals, and fixed natural tissues. All cardiovascular implants, regardless of their materials, cause some degree of thrombosis. In fact, the only nonthrombogenic surface known is the natural lining of the cardiovascular system, the endothelium. The basis of this thromboresistance is not completely understood. It is thus far known that cardiovascular endothelial cells, as well as the other components of the vessel wall, are subject to variations of blood flow and pressure with every cardiac cycle. They secrete, absorb, and transfer substances by processes involving



NHLBI photograph of a porcine heart valve.

metabolism, diffusion, and convection. Moreover, they interact with blood cells and proteins in different states of activation, depending on flow, pressure, and vessel configuration. Natural thromboresistance probably involves all of these factors. Recent studies of the interactions of blood and its components with the natural vessel wall have yielded considerable information on the temporal sequence of this interaction. Techniques in cell biology, such as monoclonal antibodies to specific proteins, and the availability of pure cultures of each type of vessel wall cell, provide an opportunity for acquiring additional knowledge about understanding the relationships between blood and the vessel wall components.

Although less is known about the interactions of blood with synthetic materials, research since 1978 has resulted in improved materials for cardiovascular implantation. Blood-material interactions, however, remain problematic in most prostheses that contact the blood. The events occurring at the blood-material interface still represent a gap in knowledge, and new interdisciplinary basic investigations are needed to examine the events at the interface between flowing blood and prosthetic surfaces. New techniques of cell and molecular biology provide opportunities for elucidating the phenomena that compromise prosthetic function.

*Viral Etiology and the Pathogenesis of Myocarditis*

In the United States, myocarditis commonly afflicts otherwise healthy

young individuals. In some patients, it can follow a progressive course to cardiac failure and death. Knowledge of the pathogenesis of the disease could lead to improved medical management and a reduction in the number of patients for whom transplantation is the only available therapy.

A considerable amount of evidence implicates viral infection as an initiating factor in many patients. However, except in the neonatal form of the disease, when infection with coxsackievirus is rapidly followed by multiple organ failure and death, a virus has rarely been isolated from hearts of patients who died with the disease. Endomyocardial biopsies have also failed to produce evidence that progressive myocyte injury is due to the direct effects of a virus. Similar observations have been made in animal models of the disease, in which immune mechanisms have been shown to play a role in the progressive form of the disease.

Basic investigations are needed on the putative role of viruses as etiologic agents in the pathogenesis of human myocarditis. In particular, studies are required to understand the immunopathology of the disease.

#### *Mechanisms of Obesity-Associated Hypertension*

Data from the second National Health and Nutrition Examination Survey (NHANES II) indicate that 16 percent of the population with normal blood pressure is obese and that 44 percent of the hypertensive population is obese. Even though obesity-associated hypertension is clearly a very serious public health problem and affects approximately 25 million Americans, relatively little is known about the mechanisms of obesity and the mechanisms of hypertension. Even less is known about the combined mechanisms of the disorders. Furthermore, present methods of weight control are limited and many obese subjects either lose no weight at all or even-

tually regain what they have lost.

Interdisciplinary research, including specialists in nutrition; physiology; pharmacology; biochemistry; pathology; endocrinology; and neural, genetic, cellular, and molecular biology is needed to elucidate the mechanisms of obesity-associated hypertension. Such information is essential for disease prevention.

#### *Atherogenesis and Aging*

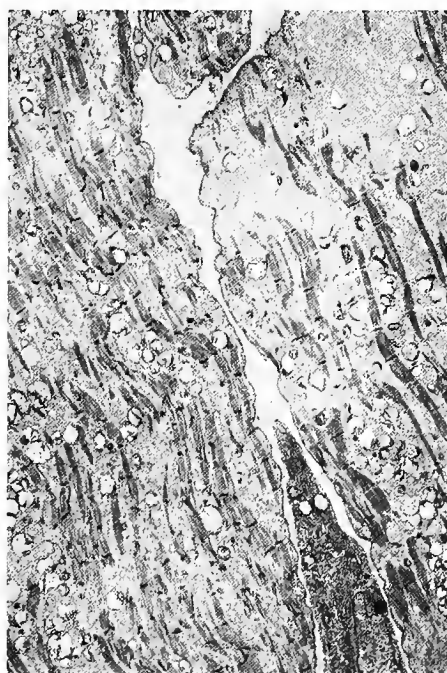
With the significant increase of older individuals in the U.S. population and the continued prevalence of cardiovascular disease, the need to better understand the interactions of biochemical changes and aging and their contribution to the initiation, progression, or regression of atherosclerosis is increasingly evident. Unfortunately, research in this area has so far been hampered by two problems. First, the number and complexity of the changes in metabolic functions that occur with aging make it difficult to identify the changes that are particularly relevant to the development of heart disease. Second, there is presently no animal model in which physical and biochemical changes due to age are well documented and in which atherogenesis can be induced. A new research objective is to elucidate the relationship of the aging process to the atherogenic process. The research would determine whether the response to atherogenic challenge or treatment is affected by age, and identify age-related changes in metabolic processes that might affect the development or regression of atherosclerosis.

#### *Effects of Postmenopausal Estrogen-Progestin Preparations on Coronary Disease Risk Factors and Osteoporosis*

Premenopausal women have a lower rate of ischemic heart disease than men of similar age. Surgically induced or early natural menopause seems to increase the risk of coronary heart disease. Women on estrogen replacement therapy, however, appear to have a lower risk of coronary heart disease than women not on estrogen replacement therapy. These facts have



*NHLBI electron micrograph of normal-sized muscle cell from boy with ventricular septal defect. (left)*



*NHLBI electron micrograph of parts of two muscle cells from the heart, removed at successful transplantation, from a teenage boy who developed severe cardiac failure after acute myocarditis. Micrograph shows loss of myofibrils, mitochondrial damage, and accumulation of glycogen. (right)*

focused interest on estrogens as possible mediators of beneficial effects, and on their relationship to atherosclerosis risk factors. A Trans-NIH Estrogen Working Group, convened by the NHLBI to make recommendations on the feasibility of a clinical trial of the effects of postmenopausal estrogen use on CHD mortality, unanimously endorsed the desirability of conducting a clinical trial, but the group concluded that the expected cost and required study size would make such an effort unfeasible. An evaluation of the effects of oral and new types of parenteral estrogen-progestin preparations on CHD risk factors (especially lipoproteins and coagulation), osteoporosis, endometrial function, and other parameters was felt by the working group to be of significant scientific importance and of potential importance to public health. Final details for the design and content of the research effort are under development by the working group. Results of the investigations are expected to provide the scientific basis that will allow clinicians to make appropriate choices related to postmenopausal estrogen-progestin therapy.

#### *Coronary Heart Disease Among Black Americans*

Available data on coronary heart disease in black Americans show different patterns of prevalence versus incidence when compared to patterns for whites. Black men, whose CHD mortality is similar to that of white men, may experience a lower incidence of nonfatal heart disease events but higher rates of sudden and out-of-hospital fatalities. Black women have CHD death rates twice those of white women. In addition, blacks are dramatically underrepresented among patients undergoing specialized cardiovascular procedures such as coronary artery bypass surgery. These patterns may reflect possible differences between blacks and whites in their recognition of CHD symptoms, in their access to and prompt use of medical treatment, and in their referral to and use of specialized treatments. Research is needed to identify the knowledge, beliefs, and behavior

among blacks regarding symptoms of acute CHD, to determine barriers that influence their seeking and obtaining appropriate medical care, and to identify the community and health care provider variables that might influence CHD treatment.

#### **Areas of Scientific Opportunity**

##### *Connective Tissue Matrix and Atherosclerosis*

Injury to the arterial cell wall is recognized as an important contributor to the development of atherosclerotic lesions. Some of the major components implicated in lesion formation include proteoglycans, fibronectin, laminin, elastin, and collagens, collectively known as arterial connective tissue components.

It has been shown that the amount of collagen produced by an arterial cell is increased in fibrous lesions despite a decline in the proliferative capacity in these lesions. The regulation of collagen synthesis in atherogenesis, however, has not been completely clarified. Factors from platelets and macrophages have been reported to stimulate collagen synthesis *in vitro*, and proteolytic enzymes have been suggested as having a role in the maintenance of collagen synthesis.

Proteoglycans occupy a large physical domain and behave as polyelectrolytes in the extracellular space. They have been implicated in atherogenesis through their regulation of tissue permeability to plasma macromolecules such as low density lipoproteins and very low density lipoproteins. Proteoglycans have been studied extensively in many tissues and fluids, and comprehensive information on their structure and function is available. There is little information, however, about proteoglycans in the arteries, and even less about the normal structure and function of the intact proteoglycans, their monomers, or their carbohydrate moieties. Even fewer studies report on the alterations occurring with the progression of atherosclerosis. It is known that as arteriosclerotic lesions progress, they are accompanied by an exten-

sive sclerotic reaction in such a way that advanced lesions are predominantly composed of connective matrix material including proteoglycans. Quantitative and qualitative distributions of the different types of these components have been described in atherosclerotic vessels. The factors responsible for initiating and perpetuating the atherosclerotic process, however, are unknown. Similarly, the mechanisms responsible for alterations in the composition and distribution of various connective tissue matrix molecules remain unknown.

This research area offers a wealth of research opportunities. Acquisition of basic knowledge will improve the understanding of atherosclerosis, pulmonary fibrosis, wound healing, liver cirrhosis, and other diseases.

##### *Congenital Heart Disease*

Of the three million births each year in the United States, between 24,000 and 30,000 babies have congenital heart disease. An unknown number of these cases are attributable to genetic factors, and because of the increasing success of surgical intervention, many of these infants survive into adulthood and may produce affected offspring. Thus, a significant increase in the incidence of congenital heart disease is expected in the coming years. Elucidation of the etiology and pathogenesis of these defects has been hampered by lack of well-formulated concepts of normal development, appropriate investigative tools, and information upon which to make extrapolations from experimental models to the human heart. Recent advances in biotechnology and instrumentation have expanded the opportunities for research into normal and abnormal cardiac development. It is now well established, for instance, that the early embryonic heart has insufficient cellular material to complete morphogenesis and that cells from other tissues migrate into the heart. Abnormal migration of cells is a possible cause of congenital heart malformations. Abnormal blood flow patterns and excessive

amounts of circulating hormones also have been implicated as possible causes. Opportunities now exist for the study of congenital heart disease in all phases of research, from molecular and cellular biology through applied research on animal models and noninvasive clinical studies designed to improve the diagnoses and treatment of congenital heart disease.

#### *Influence of Hypertension and Diabetes on the Cardiovascular System*

Considerable evidence indicates that the prevalence of hypertension is increased in the diabetic population, both in insulin-dependent and in noninsulin-dependent patients. Delineation of the nature of the association is complicated by such factors as concurrent obesity, renal involvement, type and duration of disease, therapy, and presence of vascular disease. Although it is uncertain how the two diseases are etiologically related, several factors deserve further consideration.

The higher prevalence of systolic hypertension in elderly diabetics may reflect the enhanced atherosclerosis occurring as a result of the diabetes. Diabetic nephropathy or associated complications may play a role, as well as the development of renovascular disease and secondary hypertension. Recent studies have suggested that plasma insulin and blood glucose levels can influence blood pressure regulation. A significant correlation has been reported between plasma insulin and diastolic blood pressure in patients with impaired glucose tolerance. Of interest is the fact that increases in circulating insulin levels within the physiologic range can cause sodium retention, at least on an acute basis. The rate of deterioration of renal function is increased in the diabetic patient when hypertension is present, and renal failure has been an important cause of death in such individuals. Diabetic microangiopathy and macrovascular disease and their complications appear accelerated in the presence of hypertension, but it remains to be determined whether therapy for either condition alters the course of the vascular disease. In addition, hyper-

tension and diabetes separately accelerate the development of atherosclerosis and its complications, and in combination, the effects appear to be synergistic.

Knowledge about diabetes and hypertension has progressed to a stage that provides an opportunity for a major expansion of research on the individual and combined effects of diabetes and hypertension on atherogenesis, including clinical studies as well as the use of new techniques in cell and molecular biology.

#### *Mevinolin and Other HMG CoA Reductase Inhibitors*

It is now well established that lowering blood cholesterol levels prevents coronary heart disease, but individuals with especially high cholesterol levels require vigorous efforts to reduce them. In many individuals, dietary treatment is insufficient, and drug therapy then has to be considered. Although several lipid-lowering drugs are available, none is completely satisfactory. There is therefore an urgent need for new potent, nontoxic, relatively inexpensive cholesterol-lowering agents.

A new class of cholesterol-lowering drugs, the HMG CoA reductase inhibitors, has recently emerged. Among the agents currently under development, the greatest clinical experience is with mevinolin. In one study, patients with type II hyperlipoproteinemia showed a 30 to 35 percent reduction in low density lipoprotein cholesterol. In other studies of healthy volunteers and over 1,000 patients with familial and nonfamilial forms of hypercholesterolemia, mevinolin and related compounds consistently reduced low density lipoprotein cholesterol by approximately 40 percent and total plasma cholesterol by approximately 30 percent. A small number of study participants have developed raised transaminase levels while on treatment. This finding is of uncertain clinical significance. Thus, reductase inhibitors reliably produce marked reductions in plasma cholesterol levels without short-term toxicity

and without the compliance problems associated with the only other available class of powerful cholesterol-lowering drugs.

If no serious toxic effects develop and if the Hmg CoA reductase inhibitors become generally available, they should revolutionize the clinical management of hypercholesterolemia. The powerful cholesterol-lowering effects of this class of drugs also offer opportunities to assess their effectiveness in the secondary prevention of coronary heart disease and the treatment of individuals with more moderate degree of hypercholesterolemia. They also raise the possibility of lesion regression in individuals in whom the cholesterol is lowered to levels previously unattainable.

#### *Lasers in the Treatment of Atherosclerosis*

The use of lasers in the treatment of cardiovascular disease holds promise. The objective of a number of experiments is to develop a laser energy source and delivery system, with techniques that can be employed in the operating room and ultimately in the catheterization laboratory, for removing atherosclerotic lesions obstructing coronary and other arteries. Thus far, patterns of tissue injury and ablative efficacy associated with different laser sources have been defined, and a system has been developed that permits visualization of the carotid and femoral arteries of living animals with intact circulation. Long-term, multidisciplinary investigation is needed that encompasses four major components of the system: assessment of the relative efficacy of different laser sources; evaluation of small catheter systems that will enable visualization of a lesion to be lased and also enable delivery of energy; identification of a flexible wave guide fiber that can be coupled to the laser source; and determination of energy levels needed for ablating target lesions.



## Lung Diseases Program

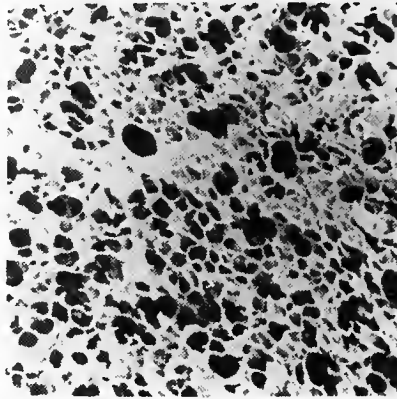
Improved effectiveness of diagnosis, treatment, and prevention of pulmonary diseases is the ultimate goal of the lung diseases research program. The program encompasses six major areas: the structure, function, and development of the respiratory system; the pathophysiology, diagnosis, and treatment of the chronic obstructive pulmonary diseases—emphysema, chronic bronchitis, and asthma; the pediatric pulmonary diseases such as respiratory distress of newborns, cystic fibrosis, and bronchiolitis; the mechanisms of occupational and immunologic lung diseases; pulmonary vascular diseases, including pulmonary hypertension, pulmonary edema, and pulmonary embolism; and the causes of and effective treatment for adult respiratory failure. Programs of education for health professionals and the lay public are developed and implemented when research advances occur that offer potential for disease prevention and treatment.

### Major Research Progress

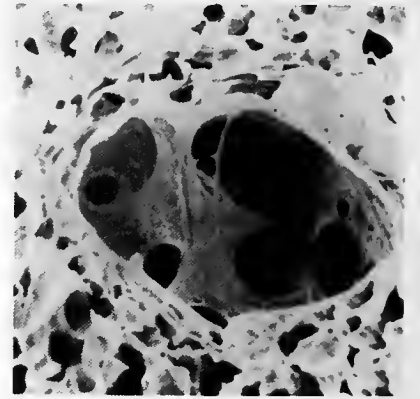
#### *Treatment of Alpha-1-Protease Inhibitor Deficiency*

Pulmonary emphysema, a chronic, insidious disease affecting over two million Americans, is caused primarily by cigarette smoking. However, approximately 2 percent of all cases occur in individuals who have a genetic deficiency of alpha-1-protease inhibitor, a protein that prevents destruction of a major structural component of the lung, elastin. During the last two decades, significant advances have been made in understanding the biochemical processes that underlie pulmonary emphysema by examining the nature of the genetic defect.

From results of these investigations, a possible approach to therapy for individuals with the genetic deficiency has been attempted by replenishing the missing protease inhibitor. The feasibility of such an approach was demonstrated recently in 21 patients with a protease inhibitor deficiency who were diagnosed with pulmonary



**Normal Lung**



**Centrilobular Emphysema**

*Damage to lung tissue caused by destruction of structural protein elastin.*

emphysema. Following administration of active plasma-derived alpha-1-protease inhibitor, blood levels rose significantly, and more important, lung protease inhibitor levels were markedly increased to normal protective levels. For these individuals, it is believed that this replacement therapy may afford at least transient protection from further destruction of lung elastin although it does not correct the genetic deficiency. The only significant adverse reactions were four postinfusion fevers from 507 infusions in these 21 individuals.

#### *Genetic Engineering for Developing an Animal Model of Emphysema*

Animal models of human emphysema are not available to evaluate long-term therapies such as alpha-1-protease inhibitor replacement for emphysema. As a first step toward developing such a model, scientists are now applying genetic engineering to create an animal model that would mimic the human genetic deficiency for alpha-1-protease inhibitor. During the past few years the genes for both the normal and the defective forms of human alpha-1-protease inhibitor have been purified and cloned. Using microinjection techniques, these genes were introduced into fertilized eggs of mice and transplanted into the uteri of suitably prepared female mice. It was shown that the human genes had become part of the genomic

package of progeny mice. The eventual aim of these experiments is to develop mice that produce defective human-alpha-1-protease inhibitor and are also deficient in their own antiprotease. These animals will be similar to the alpha-1-antiprotease-deficient humans and presumably exhibit similar susceptibility to developing emphysema.

Development of this animal model will help to better elucidate the pathogenetic processes that lead to the development of emphysema and will permit evaluation of new therapeutic approaches for familial emphysema.

#### *Sleep Apnea Syndrome*

The syndrome of adult obstructive sleep apnea is now recognized as a major life-threatening cardiopulmonary disorder characterized by cessation of breathing for longer than ten seconds, snoring, thrashing in bed, hypersomnolence, and repetitive episodes of upper airway occlusions, with reductions in arterial oxygen levels during sleep and subsequent arousal. Disordered breathing, snoring, and development of sleep apnea is predominantly seen in adult males, and is less frequently seen in premenopausal women.

Many therapeutic approaches are available. One strategy that appears to hold promise is the application during sleep of continuous positive airway pressure (CPAP) to the upper airway through the nose. CPAP, provided by a nasal mask or cannula, is thought to act by maintain-

ing a higher pressure in the pharyngeal region to avoid airway collapse during inspiration. Investigators have recently reported that CPAP relieves obstructive sleep apnea in adults, is also effective in long-term treatment, and can be safely used at home without any serious adverse side effects. A number of unresolved issues in the therapeutic use of nasal CPAP remain, however, which may be resolved only through well controlled clinical trials.

Sleep apnea is also widely seen in preterm infants. In fact, periodic breathing and an increased frequency of apneic episodes (mostly during sleep) are considered the most common respiratory control disturbances during the neonatal period. Apnea may persist in some infants until they are several months old. These apneic events can be associated with seriously low oxygen levels and marked cardiac slowing that are life-threatening and warrant treatment or monitoring.

Further studies are needed to determine the efficacy, patient acceptability, and possible side effects of CPAP for preventing upper airway collapse during sleep.

### *High Frequency Ventilation*

When a patient, for whatever reason, is unable to breathe an adequate amount on his or her own, some means of assisting breathing is required for the patient to survive, since the exchange of oxygen and carbon dioxide is essential for life.

Most of these patients are helped by ventilators, which mimic normal breathing by moving in and out a volume of air roughly equivalent to a normal breath at approximately a normal breathing frequency. However, there has recently been an interest in alternate techniques that use frequencies and volumes different from the normal pattern for healthy individuals.

One study technique is high frequency ventilation (HFV), since it appeared to offer an advantage over conventional ventilation. Over the last few years, much research has been conducted to determine whether HFV is useful in certain clinical situations. Clinical studies of HFV in adults, however, have been disappointing and HFV appears to provide no clear advantage over conventional ventilation in most situations. The one clinical area

where HFV still may produce a significant impact is in the area of support for premature babies. Promising preliminary studies of babies with little hope of surviving on conventional ventilation continue to appear, and interest in this area is growing rapidly. An ongoing multicenter clinical trial of high frequency ventilation, expected to involve 1,000 infants in ten centers in the United States and Canada, should provide needed information about whether HFV is superior to conventional ventilation for premature babies with birth weights ranging from 750 to 2,000 grams (1.5 to 4.5 lbs.).

Progress also continues to be made toward a better understanding of the physical mechanisms that control flow distribution and gas transport in the respiratory system during HFV. Studies of excised lungs have shown that the flow of gas and the transmission of pressures to various lung regions during HFV can be quite heterogeneous. The results from these studies should eventually provide a broader information base for other well focused clinical studies.

### **Research Needs**

#### *Structure, Function, and Regulation of Ion Channels in Pulmonary Epithelial and Other Cells*

Ion channels are transmembrane proteins with functions that include the coupling of external chemical, mechanical, and electrical signals to responses at the cell surface, the transmission of electrical signals, and the transport of salt and water. Ion channels form aqueous pores in cellular membranes and undergo conformational changes that result in their opening and closing, which can be regulated by several different types of signals. With the development of sophisticated recording techniques, in particular the patch-clamp method, the number of ion channels that have been described has grown rapidly. At present, detailed biochemical information on channel structure is available for only a few channels. The primary amino acid sequences are known only for the nicotinic acetylcholine



*Pulmonary technician monitors the breathing of a sleep apnea patient.*



receptor and the voltage-sensitive sodium channel. The biochemical techniques developed to study the acetylcholine receptor have facilitated the development of methods for purifying other ion channels.

Abnormalities in channel function, the number of channels, and the regulatory mechanisms that govern their opening and closing are now believed to be associated with various diseases. Aberrations in the permeability of pulmonary epithelia to chloride and sodium, for example, have been reported in cystic fibrosis. Similarly, abnormalities in pulmonary epithelial function may be associated with the altered airway secretions observed in asthma. In addition, abnormal function or response of airway smooth muscle may contribute to the airway impairment in asthma. Little is known, however, about the role of ion channels in these processes. Furthermore, the nature, function, and control phenomena for each ion channel may be different, depending on the tissue and cell in which it functions.

Further studies are required to determine the numbers, types, and chemical and physical nature of ion channels in pulmonary epithelial and airway smooth muscle cells; their regulation, modification, and aberration in health and disease; and the means by which pharmacological intervention can be designed to bring about desired changes in their functions. Research results may provide a clue to the understanding of the pathophysiology of cystic fibrosis, asthma, and possibly other pulmonary diseases.

#### *Somatic Gene Therapy for Alpha-1-Protease Inhibitor Deficiency*

Recent developments in molecular biology and genetic engineering provide a challenging opportunity to develop virus systems to deliver the alpha-1-protease inhibitor gene into hepatic cells *in vivo*. This would be a first step toward developing strategies for somatic gene therapy to correct the genetic deficiency for alpha-1-protease inhibitor—a prime risk factor for

familial emphysema. Although synthesized mainly in the liver in normal individuals, this protease inhibitor diffuses into the lung to protect it from destruction by elastase produced by inflammatory cells.

Individuals born with a genetic deficiency for the protease inhibitor synthesize an aberrant, nonsecretable protein due to a defect in the gene for the protease inhibitor. The defective gene, as well as its normal form, have been isolated and purified. This, coupled with the recent developments in genetic engineering, makes it possible to attempt to correct the genetic defect by introducing the normal gene into individuals with the deficiency. However, since the introduction of the normal gene for the protease inhibitor into the bone marrow stem cells of such an individual (a current approach for gene therapy) may interfere with functions of the progeny of stem cells, it will be necessary to develop a method to deliver the gene to the liver cells where alpha-1-protease inhibitor is actually synthesized. A virus vector can carry the gene and one possible approach for developing such a liver-specific virus vector system would be to employ a part of the hepatitis virus, which specifically infects the liver cells.

Refinement of procedures for manipulating the gene controlling the synthesis of alpha-1-protease inhibitor in deficient individuals will be a challenging area for research in the coming years.

#### **Areas of Scientific Opportunity**

##### *Immunobiology of Developing Lungs*

The transition from intrauterine to extrauterine life involves not only physiological change in gas exchange and cardiovascular function, but also an abrupt exposure of the lung to various infectious and noninfectious agents. Serious pulmonary infections occur more frequently in newborn infants than in older children and adults. They are also a leading cause of death in both full-term and premature infants. A first line of defense upon

exposure of the lung to infectious agents is provided by cells of the monocyte-macrophage series. These cells protect the host from infection by ingesting and killing microorganisms.

Alveolar macrophages directly ingest and kill microbes and, at the same time, they synthesize and secrete a variety of products that facilitate ingestion of microorganisms. Alveolar macrophages also play an important role in various aspects of the immune response, such as recognition and presentation of antigens to other cells, regulation of vascular permeability, and interaction with other cell types. At present, changes that occur in these factors during normal transition from intrauterine to extrauterine life or during intrauterine and postnatal infection are almost unknown. Also, little is known about the response to a variety of modulators of macrophage activation during this period.

Preliminary studies have suggested that the inability of newborns to mount adequate resistance to respiratory infections may be due partly to a functional immaturity of the alveolar macrophages. To understand the immunobiology of developing lungs, more research is needed on developmental phagocyte physiology.

##### *New Leads in Cystic Fibrosis Research*

Cystic fibrosis is the most frequent lethal childhood genetic disease in white Americans. The basic defect and the inborn error of metabolism are unknown, and the clinical and possibly genetic heterogeneity of the disease has complicated attempts to define the basic defect(s).

In recent years, several families, each presumably inheriting a single defective gene from a common ancestor, have been located. Availability of blood and cell samples from members of one group of families has permitted comparisons of their DNA with genetic material of other healthy individuals. Several groups of investigators, using genetic analysis by restriction fragment length polymorphism, have established linkages of the cystic

fibrosis gene to various markers on chromosome 7. In contrast, a similar study conducted by a different group of investigators on a separate family provided evidence for linkage of the cystic fibrosis gene to a genetic marker on the short arm of chromosome 21. Whether more than one gene is involved in cystic fibrosis thus remains an open question.

Location of the cystic fibrosis gene to less than 1 percent of the human genome, and its linkage, in a majority of studies, to a DNA fragment on chromosome 7 should allow studies to isolate, characterize, and clone the gene and lead to the elucidation of the perturbed biochemical pathway and help design better means for therapeutic intervention and management. In the meantime, identification of markers more closely linked to the cystic fibrosis gene will allow prenatal diagnosis in certain at-risk families.

#### *Neurobiology of Cardiopulmonary Control*

The central nervous system has an important role in the continuous regulation of cardiovascular and respiratory activity. Its influence is through a number of mechanisms that control the amount and pattern of discharges of neurons to the heart and blood vessels, alter the neural output from the respiratory centers to the neurons that innervate the respiratory muscles, couple the cardiovascular and respiratory systems to behavior, and control the release of various neurotransmitters and neuromodulators that regulate circulation and respiration.

Recent studies of the central nervous system in cardiopulmonary control have benefited from the application of various techniques of contemporary neuroscience. For example, immunohistochemical staining techniques, used to map and study the distribution of central pathways through which the brain controls circulation and respiration, have revealed that specific brain areas are dedicated to cardiovascular and respiratory control. Ongoing studies are attempting to determine if these major areas

within the brain overlap in function, or if they are separate integrative areas for control of circulation and respiration. Investigators have begun to identify some of the chemical messengers produced by neurons within these networks.

A wealth of opportunities now exists for research on central nervous system control of the cardiopulmonary systems. They range from studies to understand the very basic neural substrates underlying the cardiovascular and respiratory centers, to clinical studies linking various neurotransmitters, and to effective drug therapies for cardiopulmonary disorders.

#### *Basic Mechanisms Underlying Occupational Airway Diseases*

More than 200 organic and inorganic substances are known to cause occupational airway diseases. With the constant introduction of new materials into industry, this list will continue to grow. Some industrial substances are extremely reactive and produce strong immediate irritant effects on the airways and lungs. Others are clearly allergenic and stimulate an undesired pathologic immune response. Still others are pharmacologic stimulants that exert their effects by eliciting release of potent biologically active molecules, which in turn produce chronic pathologic changes in the respiratory system. But, for a vast majority of industrial substances either associated with, or suspected of, causing airway diseases, the pathogenetic mechanism is unknown. In addition, the mechanisms of late asthmatic reactions and nonspecific bronchial hyperreactivity are not well understood. More direct means of examining the processes that initiate occupationally induced asthmatic reactions and nonspecific bronchial reactivity are needed.

A virtually unexplored research avenue to understanding occupational airway disease is the application of bronchial lavage and bronchial biopsy to correlate changes in bronchial mucosa and submucosa with the release by airway cells of biological mediators in reaction to inhaled substances. Findings de-

rived from the application of new advances in the measurement of chemical mediators of inflammation, when coupled with a better understanding of cellular and tissue interactions in inflammatory processes, may yield important new results in research on occupational airway diseases.

### **Blood Diseases and Resources Program**

The blood diseases and resources program plans and supports research on the causes, prevention, and treatment of genetic and acquired disorders of the blood, as well as research designed to ensure an adequate and safe supply of high quality blood and blood products.

The Institute's hematology program is organized into four areas: bleeding and clotting disorders, red blood cell disorders, sickle cell disease, and blood resources. Within each of these areas, investigations encompass the spectrum of medical research, from basic laboratory findings to applications in clinical medicine. Because the functions of the blood are so closely related to heart, lung, and blood vessel diseases, increases in understanding the mechanisms and treatment of blood disease benefit all the program areas of the NHLBI.

#### **Major Research Progress**

Highlights of major research advances in the blood diseases and resources program are provided below.

##### *Progress Toward Curing Patients With Severe Beta-Thalassemia and Sickle Cell Anemia*

Major advances have been achieved toward the long-range objective of curing patients with severe beta-thalassemia and sickle cell anemia. The most promising therapeutic approach involves the transfer of functional globin genes into hematopoietic stem cells. Results of experiments to determine the most suitable vehicle for globin gene transfer have demonstrated progress. Investigators have designed a globin retroviral vector that contains

an intact globin gene with its own transcriptional control signals. When introduced into erythroid cell lines, the gene exhibits normal regulation and is expressed at a high enough level to improve globin synthesis in thalassemia patients and to inhibit polymerization of sickle hemoglobin. Preliminary results from animal studies show that gene therapy for these patients is a realistic research goal and that an effective therapy may be possible in the near future.

#### *Viruses and Bone Marrow Failure*

The B19 human parvovirus was discovered serendipitously in the sera of normal blood donors, and a large proportion of healthy adults have now been found to have evidence of prior infection. Acute B19 human parvovirus infection in children was first associated with aplastic crises of sickle cell disease. Subsequently, the viruses have also been implicated in bone marrow failure and in other circumstances. Basic information about the B19 human parvovirus may prove useful in determining specific viral etiologies of some hematologic diseases. B19 human parvovirus may also be related to other more chronic rheumatologic and hematologic diseases. Studies in tissue culture have revealed a highly specific interaction between B19 human parvovirus and a single class of hematopoietic progenitor cell.

B19 human parvovirus was recently propagated in suspension cultures of erythroid bone marrow obtained from patients with hemolytic anemia. This advance will facilitate studies to define the molecular events associated with B19 human parvovirus replication. Additional information about the molecular basis of the erythroid specificity of B19 human parvovirus may prove useful in designing vectors for gene therapy for certain hematologic diseases.

*Inactivation of Human T-Cell Lymphotropic Virus Type III and Non-A, Non-B Hepatitis Virus*  
Screening for HTLV-III antibody in all donated blood is the primary means of avoiding the transmission

of the AIDS-related virus by blood and blood products. However, there are theoretical reasons to believe that not all infected blood can be detected by this methodology. Commercial manufacturers, therefore, rely on heat treatment of factor VIII preparations to destroy any human T-cell lymphotropic virus type III (HTLV-III) infectivity. Unfortunately, these procedures have not been completely effective in simultaneously inactivating non-A, non-B hepatitis (NANB) agent(s). Cases of post-transfusion NANB hepatitis have been reported in humans who received preparations of heat-treated factor VIII.

A recently developed procedure to inactivate HTLV-III in blood products has potential application in the preparation of safe, effective blood derivatives. In factor VIII preparations, to which HTLV-III was added, treatment with tri(n-butyl) phosphate and sodium cholate resulted in complete destruction of HTLV-III infectivity in 20 minutes. Equally impressive results were obtained when the procedure was applied to the inactivation of non-A, non-B hepatitis virus in blood derivatives. This new chemical inactivation procedure not only destroys HTLV-III and NANB hepatitis viruses but also has little effect on the stability of factor VIII. It may thus serve as an alternative to heat treatment, which has been shown to reduce the biologic activity of factor VIII preparations. This new viral inactivation process has recently been approved by the Food and Drug Administration.

#### *A Synthetic Vaccine for Acquired Immune Deficiency Syndrome*

The need for a vaccine to prevent AIDS is an important priority. The development of a synthetic peptide that elicits the formation of antibody to the envelope of human T-cell lymphotropic virus type III (HTLV-III) is an important recent advance toward such a vaccine.

A synthetic peptide containing amino acid residues of the precursor envelope protein of HTLV-III has now been synthesized and used to elicit antibody in rabbits. The rabbit

antisera reacts with the envelope protein of HTLV-III and preliminary data indicate that the rabbit antisera partially inhibit HTLV-III infectivity *in vitro*. Human sera from AIDS patients and sera obtained from chimpanzees experimentally infected with HTLV-III also react with the synthetic peptide. If the peptide vaccine is found to be effective in preventing HTLV-III infection in chimpanzees, the animals will be subsequently rechallenged to determine the extent and duration of immunity. After these safety and efficacy studies, clinical trials may be initiated among humans.

#### *Penicillin Prophylaxis in Sickle Cell Disease*

Overwhelming pneumococcal infection continues to be the major cause of death in infants afflicted with sickle cell anemia. Ten to 12 percent of infants with sickle cell disease develop such infection and the mortality ranges as high as 35 percent. A multicenter, randomized, double-blind, placebo-controlled clinical trial designed to test whether regular daily administration of oral penicillin reduces the incidence of septicemia resulting from *Streptococcus pneumoniae* in children with sickle cell anemia under the age of 3 years was completed 8 months early after an average of 15 months of treatment. An 84 percent reduction in the incidence of infection was achieved, with no fatalities in the penicillin-treated group. On the basis of these compelling positive results, it is recommended that children be screened in the neonatal period for sickle cell disease and that those afflicted be placed on daily oral penicillin by 4 months of age.

These recommendations should have a major impact on the management of infants and children with this illness. If the recommendations are followed, the incidence of pneumococcal septicemia among these patients can be decreased by 90 percent and possibly eliminate this infection as a cause of death in this age group.



*Testing of young infant and sickle cell counseling of parent.*

#### *Development of Drugs for Sickle Cell Disease*

Currently, there is no effective therapeutic agent to prevent the progression of sickle cell disease. Although a number of agents capable of interfering with the polymerization of hemoglobin S have been described in the literature, efficacy has not yet been demonstrated *in vivo* for any of them. Many are either toxic, do not cross the red cell membrane, or their low level of efficacy *in vitro* makes them unsuitable for clinical use. Among the various strategies that have been proposed to inhibit intracellular polymerization, the most straightforward appears to rely on small molecules that can bind to regions of the hemoglobin S molecular surface involved in an intermolecular bond in the polymer. The design of such stereospecific inhibitors should be aided by a detailed knowledge of these surface regions.

Research should now take advantage of this new knowledge for the design, synthesis, and development of drugs and therapeutic approaches that may be effective in

the treatment of sickle cell anemia. Possible approaches include altering the sickle hemoglobin molecule, modifying the red cell volume, or increasing the synthesis of fetal hemoglobin.

#### **Research Needs**

##### *Natural History of Post-Transfusion Non-A, Non-B Hepatitis*

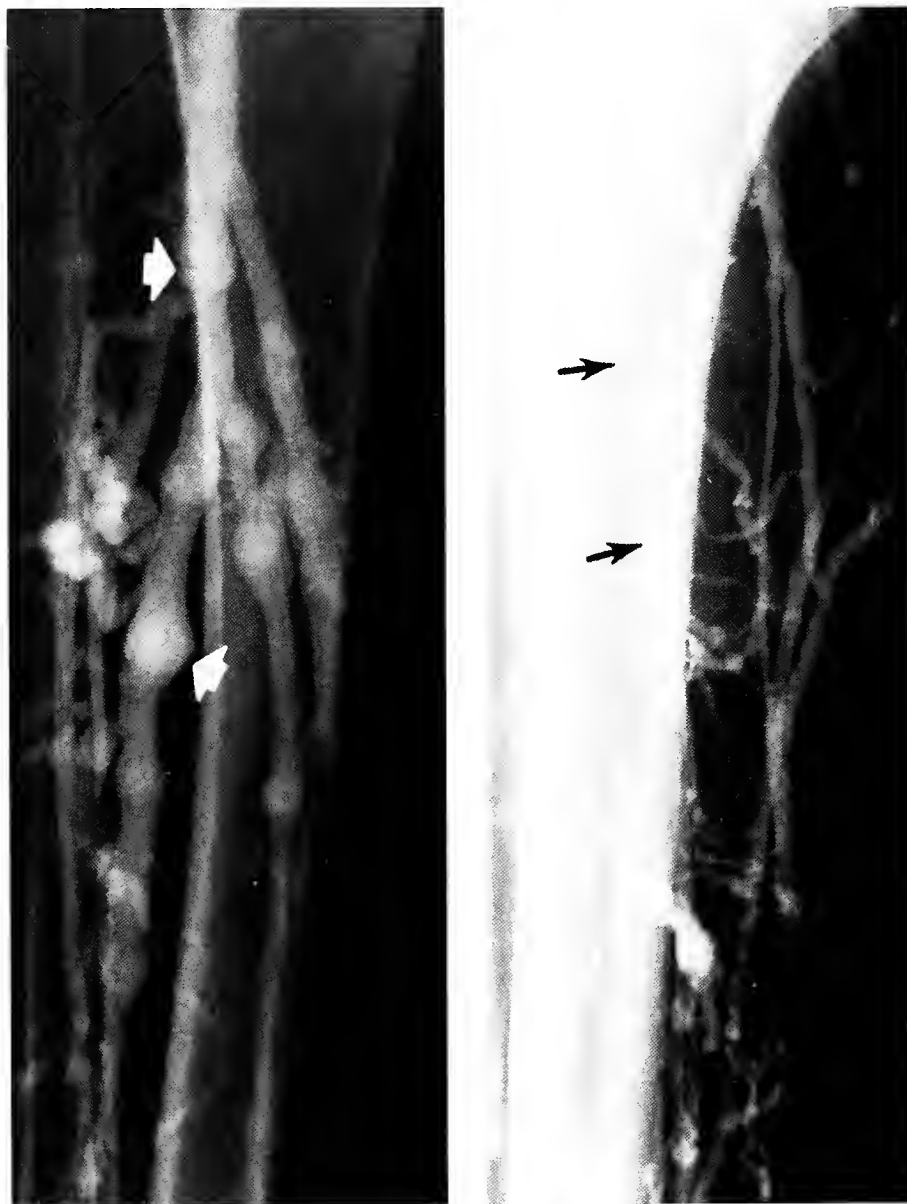
Hepatitis following the transfusion of blood and blood products continues to be an important problem, despite routine screening of donor blood for hepatitis surface antigen (HBsAg). It has been estimated that 7 to 10 percent of transfused individuals develop post-transfusion hepatitis, and the majority of the cases are ascribed to the virus(es) of non-A, non-B (NANB) hepatitis. Because the viral agent or agents responsible for NANB hepatitis have not yet been identified, it is not presently possible to prevent the illness.

Of even greater concern is the finding that chronic hepatitis appears to be a common result of

acute NANB post-transfusion hepatitis. In a recent survey of reports on NANB post-transfusion hepatitis, chronic hepatitis was found to have developed in 10 to 17 percent of the acute hepatitis patients, in 44 percent of persons with hereditary coagulopathies, and in 28 percent of renal transplant patients. Thus, it appears likely that chronic liver disease occurs at least as commonly, and perhaps more commonly, following infection with the NANB virus(es), than following infection with the hepatitis B virus. Further information suggests that the presumed serious histopathologic abnormalities of chronic active hepatitis and cirrhosis are also more common than previously believed. In addition, the ultimate outcome of these complications is not yet well established. In fact, the chronic sequelae of NANB hepatitis infection may be more serious than the acute illness. Because data on the disease have been derived primarily from isolated studies and the conclusions are not clear-cut, the problem of chronic NANB hepatitis should be studied on a wider scale. A long-term evaluation of large numbers of individuals with chronic NANB hepatitis is needed. The data would permit the development of conclusive information regarding the clinical, biochemical, and histologic outcome that would improve the management of this disease.

##### *New and Improved Instrumentation for Diagnosis of Deep Vein Thrombosis*

Venous thromboembolic disease has long been recognized as a serious complication in both medical and surgical patients and occasionally can affect ambulatory and otherwise healthy individuals. It is responsible for at least 95 percent of pulmonary emboli and is a potentially fatal disorder. In 1983, the cost of hospital care alone for this disorder exceeded \$500 million. In addition, the economic impact of misdiagnosis and inappropriate treatment of deep vein thrombosis is considerable. Currently, venography is considered to be the only direct method for definitive



Normal calf venogram: x-ray opaque material fills all vessels. Note normal valves (white arrows). (left)

Venogram of patient with acute deep vein thrombosis of the leg: x-ray opaque material fills smaller, superficial veins, but there is minimal filling of large, deep vessels, and there are clots (dark arrows). (right)

assessment of the presence and extent of acute venous thrombosis, but the procedure is lengthy and expensive. It also causes moderate discomfort to patients and can result in adverse side effects. Techniques that have been applied to the detection of plaque in arteries, such as ultrasonic methods and magnetic resonance imaging,

are potentially capable of detecting deep vein thrombosis. Research is needed on the development and evaluation of new and improved techniques to detect and quantify venous obstruction, including deep vein thrombosis, to detect and quantify blood flow in peripheral veins, and to estimate the age of thrombi.

## Areas of Scientific Opportunity

### *Omega-3 Fatty Acids and the Mechanisms of Thrombogenesis and Atherosclerosis*

Epidemiologic studies have shown a lowered incidence of thrombosis and coronary heart disease among certain populations, such as Greenland Eskimos and Japanese fishermen. The low incidence has been related to their unusual diet, which has traditionally consisted of seals, whale, and fish. These marine products contain an unusually high content of eicosapentanoic and docosahexaenoic acids, which are omega-3 fatty acids. In populations in which marine-derived products do not form an important part of the diet, the principal polyunsaturated fatty acid is arachidonic acid, which is an omega-6 fatty acid. Preliminary information indicates that the metabolic products of prostaglandin metabolism that result in the presence of omega-3 eicosapentanoic acid (EPA) differ from those produced when omega-6 arachidonic acid is available. EPA-induced changes in platelet function, such as aggregation and adherence, have been confirmed. Other reports link EPA to changes in plasma lipids and lipoproteins, blood pressure, and cell-mediated immunity. In none of these areas, however, has extensive research been undertaken. Nevertheless, dietary recommendations for a certain number of fish dishes per week have begun to appear in both the lay and scientific press. Building upon this preliminary base of knowledge concerning the effects of EPA, focused studies are needed to elucidate the mechanisms of these various biological processes and their clinical implications. Such studies are needed to form the basis for possible dietary recommendations pertaining to the prevention or modulation of thrombosis and atherogenesis.

### *Effectiveness of Antibody Screening for Acquired Immune Deficiency Syndrome*

The first case of AIDS resulting from blood transfusion was reported in 1982. Since then over 300 cases of transfusion-associated AIDS have been reported. Enzyme-linked immunoassay (EIA) systems to detect antibody to HTLV-III were licensed in March 1985, and the tests are now used throughout the United States for routine screening of blood donors. Disturbingly, in more than one year's experience with EIA, there have been some individuals from whom HTLV-III has been isolated who do not have detectable antibody to the virus. Even though the frequency of such false negative tests in apparently healthy donors is probably very low, the few that may occur could have serious repercussions. Such a possibility suggests that assays other than those to detect antibody to HTLV-III may be needed to identify all infected individuals. An opportunity now exists to study the effectiveness of the present anti-HTLV-III screening procedures and to determine the magnitude of this potential problem.

### *Preparation of Immunoglobulin Against Acquired Immune Deficiency Syndrome*

Research is under way to develop an immune globulin preparation that may help in the prevention of AIDS in certain populations. Investigators are testing the sera of male homosexual volunteers for neutralizing antibodies to HTLV-III. Adequate concentrations of virus-neutralizing activity have been demonstrated so that it is now possible to collect and pool large quantities of plasma and to develop an investigational product suitable for clinical trials. The immune globulin preparation will then be tested in appropriate animal models for safety and efficacy. Once the safety and efficacy of the preparation are established, clinical studies in selected human populations will be considered.

### **Conclusion**

The Institute seeks to meet its goals of better health for America through research leading to better diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases.

The Senate Committee on Appropriations for the Departments of Labor, Health and Human Services, and Education and Related Agencies reported in 1985: "The Committee is pleased that the Institute continues to support a multifaceted research and education program that includes basic and clinical research, a centers program, clinical trials prevention and education efforts, as well as research training and career development. This diverse and balanced approach is required because of the magnitude of the multiple disease problems addressed by the Institute and because of the unevenness of our knowledge of these diseases and the treatment of patients who have them."<sup>4</sup>

*(4) 99th Congress, 1st Session, Report 99-151, p. 62.*

## **The Biennial Report of the Director, National Institute of Dental Research**

### **History**

The following events represent milestones in the development of the National Institute of Dental Research (NIDR).

- 1931—PHS created a Dental Hygiene Unit at NIH.
- June 24, 1948—The National Dental Research Act (P.L. 80-755) created the National Institute of Dental Research and the National Advisory Dental Research Council.
- January 10, 1949—The first meeting of the National Advisory Dental Research Council was held. The Institute-supported grants program was initiated and the first grants and fellowships awarded.
- October 30, 1954—The first meeting of the Board of Scientific Counselors was held. This board was established to provide advice to NIDR on matters of general policy, particularly from a long-range viewpoint, as they relate to the intramural program.
- 1958—The President signed an appropriations bill that included provisions to finance construction of a building for the Dental Institute.
- 1966—A major reorganization of the Institute's extramural program was implemented to plan and support more adequately research and training programs designed to attack the major dental diseases and concerns—dental caries, the periodontal diseases, oral-facial anomalies, and biomaterials.
- 1967—An NIDR program of grant support was initiated for the development of several dental research institutes/centers in university environments. This program was designed to utilize all of the appropriate resources of the parent universities to create ideal research and training environments, fostering interdisciplinary approaches to the complex problems of oral diseases and disorders.



• 1971—The National Caries Program was launched, utilizing funds earmarked to accelerate development of preventive methods to reduce tooth decay.

• 1975—Having established the safety and efficacy of several caries preventive measures, the NIDR initiated selected school-based demonstration projects through its National Caries Program.

• 1983—Dr. Harald Loe was appointed Director of the Institute.

• 1983—The NIDR opened the first multidisciplinary pain clinic in the United States devoted exclusively to research. The clinic provides an opportunity for all NIH researchers and clinicians to pool their knowledge and exchange ideas about the pathophysiology and treatment of pain.

The Institute initiated an annual honorary lecture to recognize outstanding scientific accomplishment in basic and clinical research and to honor distinguished scientists who have made important contributions in areas of research directly related to the interests of the Dental Institute. The lecture, given each September at the NIH campus, is now called the Seymour J. Kreshover Lecture Award.

• 1984—An NIDR reorganization disbanded the National Caries Program and created the Epidemiology and Oral Disease Prevention Program (EODPP). The EODPP is devoted to research on the etiology, incidence, and prevalence of dental caries, periodontal diseases, and other oral diseases and disorders.

## Introduction

The NIDR supports research and research training on the cause, prevention, diagnosis, and treatment of oral, dental, and craniofacial disorders and related systemic conditions. Its programs include clinical and laboratory research aimed at the eradication of the two major oral diseases—tooth decay and the periodontal diseases as well as research on a broad variety of conditions affecting oral soft and mineralized tissues. The Institute

conducts research and engages in research training through both its Intramural Research Program, a collection of laboratories and clinics on the NIH campus, and the Extramural Research Program, which awards grant and contract funds to the scientific community.

Dentistry was little more than a trade when NIDR was created almost 40 years ago. Today it's a burgeoning, influential discipline with important ties to nearly every branch of medicine. Dentists are becoming "physicians of the mouth," diagnosing and treating a wide range of disorders with oral manifestations. And dentistry is one of the few health professions poised to become largely a discipline of prevention.

What happened to produce such a transformation? The turning point came about 30 years ago when dental researchers proved that the two most prevalent oral problems—tooth decay and the periodontal diseases—are infectious disorders. These findings propelled dental science into the mainstream of biomedical research. They also revolutionized dentistry. Tooth loss was no longer considered an inevitable consequence of aging, but rather the result of disease that could be diagnosed, treated, and ultimately prevented.

Today, oral health science is not only part of mainstream biomedical research, it has moved to the fast track. Dental scientists have been quick to adopt the new techniques of cell and molecular biology, particularly recombinant DNA and monoclonal antibody methods. With these new tools, they are rapidly advancing our knowledge of fundamental mechanisms underlying oral health and disease. The "molecularization" of dental research is also accelerating the transfer of laboratory findings into clinical applications.

From an initial focus on caries and the periodontal diseases, NIDR research has grown to encompass the full spectrum of oral health concerns. As oral health research has expanded, so have its benefits. Dental scientists are discovering mechanisms of cell function com-

mon to many tissues. Their work is contributing to our understanding of cancer, arthritis, diabetes, heart disease, musculoskeletal disorders, congenital defects, acquired immune deficiency syndrome (AIDS), and other health problems.

The payoffs of NIDR research have been great. Tooth decay, which has plagued mankind throughout the 3,000 years of recorded history, is declining for the first time. A third of American children are now caries-free, and the rate of tooth decay among the remaining children has been cut in half over the past generation. In 1 year alone—1981—the resulting savings in the Nation's dental bill amounted to \$2 billion, about twice the total budget allotted to NIDR throughout its history.

The following report describes selected advances in NIDR research during FY 1985 and 1986. It also discusses research training initiatives, special meetings sponsored by the Institute, and science transfer activities during that period.

## Dental Caries

Tooth decay has been the unwelcome companion of man since before the time of recorded history. Through the ages, many a colorful theory has surfaced to explain what causes dental caries. Not until the beginning of this century, however, did the truth begin to emerge that decay results from acids in the mouth. It was not until 30 years ago that NIDR experiments proved that caries is an infectious disease, caused by acid-producing bacteria.

## Fluoride

Other early NIDR studies confirmed the value of fluoride in protecting teeth from decay. Fluoride—a naturally occurring mineral found in drinking water throughout the world—not only protects tooth enamel from attack by bacterial acids, but also stimulates remineralization, reversing the course of decay during the early stages of caries. Today about 7,000 American communities, representing over one-half of the U.S. population,



have adopted municipal water fluoridation programs. In addition, an estimated 13 million children participate in school-based fluoride programs.

Nelson County, Virginia, operates the oldest school-based fluoride program in the country. When NIDR initiated the program 14 years ago, the oral health of the school-age population in this rural, economically depressed area was poor. Part of the problem was that the area's drinking water has a very low concentration of fluoride. An intensive prevention program, involving the use of three fluoride agents (dentifrice, daily tablets, and weekly mouth rinses) has reduced the prevalence of tooth decay among Nelson County's schoolchildren by 65 percent.

In 1972, only 15 percent of the children were caries-free. Today, 40 percent have no cavities. Moreover, at the outset of the study, 12 percent of the students examined had rampant caries—21 or more decayed, missing, or filled tooth surfaces. Now, fewer than 1 percent have this cavity rate. The investigators have recently added sealants to this prevention effort with an eye toward eliminating tooth decay altogether from Nelson County.

### Sealants

The rate of tooth decay among American children has been cut in half over the past generation. Much of this decline is attributable to fluoride. To further protect teeth from decay, NIDR-supported scientists have developed adhesive sealants. These plastic films are painted over the chewing surfaces of teeth, effectively sealing out decay.

Sealants are not yet used routinely by most dentists because of concern that incipient carious lesions present at the time sealants are applied might progress underneath. A recent study by NIDR grantees not only showed that caries does not progress, but also provided evidence that dental sealants can promote the natural repair of small carious lesions. Thus, there is considerable promise that dentists will be able to avoid costly and tooth-damaging filling procedures by the simple use of sealants.



*An NIDR clinical investigator applies a protective dental sealant to the chewing surfaces of a child's molars. Sealants provide maximum protection against tooth decay when used in combination with fluorides.*

NIDR scientists realized a long-term goal last year by designing a sealant that releases a steady flow of fluoride. Sealants and fluorides in combination have the potential to prevent virtually all dental caries in children. Researchers are now testing the new sealant to determine the optimal rate of fluoride release.

### "Super Saliva"

Other NIDR grantees are working on a synthetic "super saliva" that could repair incipient carious lesions before they become overt cavities. These researchers have shown through microscopy that the typical person has at least 20 carious lesions too small to be seen by current diagnostic techniques. Most of these will never develop into cavities, but will become remineralized. By the time a carious lesion is detected, the researchers say, it may have existed below the tooth surface for about 3 years.

Acids produced by bacteria in the mouth dissolve tooth mineral. Saliva contains minerals—calcium and phosphate—that rebuild the tooth. When the rate of mineral breakdown

exceeds the rate of remineralization, tooth decay results. The investigators are trying to develop a solution of calcium, phosphate, and fluoride that can outperform even saliva at remineralizing incipient carious lesions. Such a solution could be marketed as a mouth rinse.

### Periodontal Diseases

As aggressive anticaries measures become increasingly widespread, larger numbers of young people will withstand the threat of tooth decay—only to confront possible attack by periodontal diseases later. In the United States, gum disorders are endemic, affecting approximately 94 million people. Because periodontal diseases destroy the connective tissue and bone that support the tooth, these diseases are a primary cause of tooth loss after age 35.

### Immune Cell Defects

Periodontal disease research is benefiting from a concentrated study of relatively rare diseases that affect young people: juvenile periodontitis and prepubertal periodontitis. Both diseases appear to involve specific inherited defects in a critical host

defense cell, the polymorphonuclear white blood cell. These findings have given rise to a five-site collaborative clinical study to shed light on the familial nature of these periodontal disorders and to aid in identifying individuals at risk.

The discovery of abnormalities in the neutrophil—the body's major line of defense against bacteria—may explain the increased susceptibility of some persons to severe periodontal infection, particularly localized juvenile periodontitis (LJP). The findings by extramural investigators point to a familial defect in the neutrophil's ability to move quickly to the inflammation site, where it normally kills invading microorganisms. In LJP patients, this important protective cell does not respond properly to chemical distress signals sent by the inflamed tissues, giving harmful bacteria the opportunity to become well-entrenched. Studies are continuing in an effort to identify the key factors involved in both normal and defective neutrophil movement to the infection site, and to design treatments to correct this impaired cell function.

### Home Treatment Comparison

The first line of defense against periodontal infections is an effective home treatment regimen for removing plaque from teeth. Two hundred thirty-one persons with early to moderate periodontitis took part in an extramural research project that compared two home treatment regimens on three major points: reduction in infection-causing bacteria, clinical improvement, and patient compliance and acceptance. The results of the 2-year study have shown that for each of the three areas of focus, regular use of a salt and peroxide regimen is no more effective than a daily program of toothbrushing and flossing in reducing the signs and symptoms of periodontal disease.

### Diabetes and Periodontal Disease

Periodontal disease is a frequent complication of diabetes mellitus. To help unravel the complex interactions of these two disease processes, NIDR-supported dental scientists are

collaborating with diabetes experts in Phoenix, Arizona, to study the Pima Indians—a native American tribe with the highest rate of diabetes in the world. The findings show that in this group, markedly severe periodontal disease is an early and common complication of noninsulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes. The research team also found that the gum disorder appears to be associated with *B.gingivalis*, an organism most strongly suspected of causing periodontal disease, and that one-third of the diabetics have lost all of their teeth—most likely due to this form of periodontal disease. Future studies will focus on a broader understanding of the causes of periodontal diseases, on better approaches to treatment, and on the ultimate prevention of this serious complication of diabetes.

### X-Rays of the Future

Periodontists in the not-too-distant future will be able to measure minuscule changes that occur over time in teeth and supporting oral tissues with a new computerized x-ray process. NIDR intramural scientists have developed a prototype Digital Subtraction Radiography (DSR) system that produces faster, more accurate images with less radiation exposure than that produced by existing dental x-ray techniques.

The DSR system employs a highly sensitive x-ray scanning device that is positioned outside the mouth. A digital computer controls the device, allowing it to scan portions of the mouth continuously. Inside the mouth is a miniature video imaging system that produces three-dimensional pictures of the area being scanned. Numerous images can be produced without exposing the patient to more radiation than he would receive in a single, conventional dental x-ray. The image can be viewed immediately and stored on magnetic tape for later review. The computer allows the diagnostician to view composite images simultaneously, then to "subtract"

individual images, allowing closer inspection of those remaining.

Tiny changes in teeth and supporting tissues, until now undetectable, are visible with the new technique. The DSR system will make possible early diagnosis of a variety of dental disorders, including periodontal disease, bone loss, and caries. It will also allow dentists to evaluate the effectiveness of treatment for those disorders.

### Pain Research

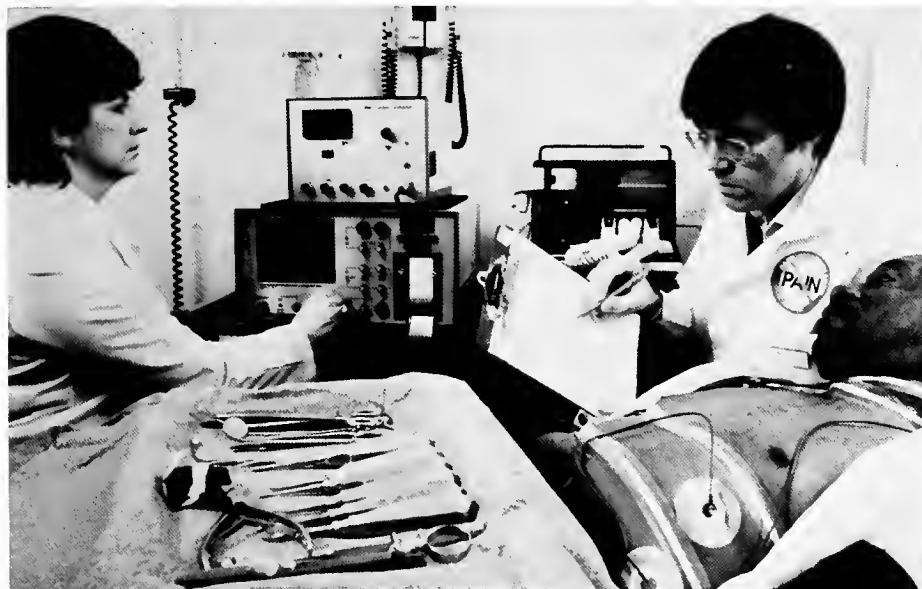
Three years ago, NIDR established the country's first multidisciplinary pain clinic devoted exclusively to research. The Pain Research Facility is located in NIH's research hospital. There, NIDR staff—in collaboration with researchers from other NIH Institutes—investigate the causes, measurement, and treatment of a variety of acute and chronic pain conditions. Current studies involve patients with diabetic neuropathy, post-herpetic neuralgia, cancer, myofascial pain, lower back pain, and tension headache.

### Diabetic Neuropathy

More than a million Americans with diabetes suffer from diabetic neuropathy, a chronic pain condition caused by nerve damage, usually in the feet, legs, or hands. The pain associated with this condition can be disabling. In studies under way in NIDR's pain clinic, investigators have proven that a drug called amitriptyline, which is normally used to treat depression, relieves the pain of diabetic neuropathy and allows patients to resume normal activities.

### Pain Relief

NIDR researchers in the Pain Clinic are studying a variety of drugs for use in pain modification. They recently found that ibuprofen—the ingredient in Motrin, Advil, and Nuprin—effectively suppresses the pain and inflammation of rheumatoid arthritis. They also found that flurbiprofen, a closely related drug, does a better job of relieving pain following oral surgery than do the currently used drugs. Patients experience fewer side effects with flurbiprofen, and dentists report no interference with bleeding times or clotting.



Researchers at the Pain Research Clinic study the use of various drugs to determine which are the most safe and effective in relieving pain and anxiety. Here, NIDR researchers are measuring a patient's physiological and psychological responses to an intravenous drug given prior to oral surgery.

### Corticotropin Releasing Factor

In a preliminary study, NIDR Pain Clinic scientists have shown that patients who received extra amounts of the natural hormone corticotropin releasing factor (CRF) following removal of their wisdom teeth experienced a reduction in perceived pain. CRF is secreted by the brain and controls the pituitary gland, often referred to as the body's master gland. Not only does the pituitary regulate such functions as growth, reproduction, and metabolism, but it also controls the body's ability to adapt to stress. When the body encounters stress such as surgery, CRF stimulates the pituitary to secrete several hormones, including beta-endorphins—natural substances 20 to 100 times stronger than morphine in relieving pain. The investigators found that administering additional CRF to patients increased the levels of beta-endorphins, and significantly reduced postoperative pain.

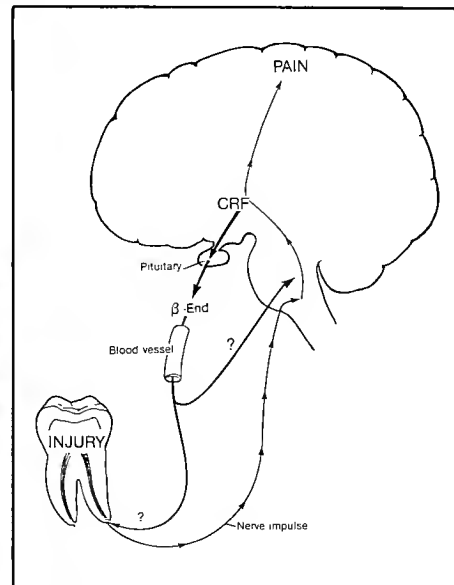
### Transcutaneous Electrical Nerve Stimulation

In preliminary tests, NIDR grantees have shown that a simple technique called transcutaneous electrical nerve stimulation (TENS) controls the

discomfort and pain associated with typical dental treatments. Resembling a small radio with headphones, the TENS device was more than 90 percent effective in relieving pain from placement of dental fillings. TENS also alleviated, in all patients, discomfort caused by removal of calculus or calcium deposits beneath the gums. Most significantly, this technique effectively controlled pain in two-thirds of patients undergoing tooth extractions.

### Soft Tissue Diseases

Dental scientists view the mouth as a complex assemblage of mineralized tissues — teeth and jaw bones—and varied soft tissues, including the lips and gums, tongue and palate, salivary glands, and other specialized tissues of the oral cavity. NIDR's research focus on the soft tissues is aimed at new treatments, permanent cures, and preventive measures for a wide array of disorders that range from local irritations to life-threatening cancers. Oral cancers are of major research interest at NIDR, and investigations into the roles of viruses, fungi, and other factors in their development are targeted objectives of the Long-Range Research Plan. Oral cancers occur at a rate of



NIDR investigators are studying the hormone beta-endorphin (B-End) and its role in pain relief. The process begins with the secretion of corticotropin releasing factor (CRF) by the brain. CRF controls the pituitary gland and stimulates it to secrete beta-endorphins in response to stress. B-End then circulates throughout the bloodstream and may act to relieve pain either at the site of injury or in the brain.

26,000 cases a year in the United States, and account for 9,000 deaths annually.

### Smokeless Tobacco

NIDR has been exploring the links between tobacco use and soft tissue malignancies. In 1986, a scientific consensus panel convened by NIDR in collaboration with the National Cancer Institute concluded that the public should be warned that the use of smokeless tobacco, particularly snuff, increases the risk of oral cancer. Other health problems associated with smokeless tobacco use include localized gum recession and leukoplakia (a precancerous condition) where the snuff is usually placed. Moreover, use of these products releases nicotine into the bloodstream and produces blood levels of nicotine comparable to those produced by cigarette smoking. The results of regular use are

long-term nicotine dependence and its associated health risks, including possible cardiovascular risks due to elevations of blood pressure, heart rate, and certain blood lipids and hormones.

#### **Prevention Protocol**

NIDR intramural investigators reported successful results using a new protocol to help cancer patients avoid the oral health problems that often result from treatment with radiation and chemotherapy. The prevention program uses a slide show to educate patients on the oral health consequences of cancer treatment. In addition, NIDR dentists conduct oral evaluations of NIH cancer patients before, during, and after treatment, and encourage vigorous oral hygiene regimens.

Patients undergoing chemotherapy are at risk of developing bleeding in the mouth, inflammation of mucous membranes, and serious oral infections. Chemotherapy and radiation to the head and neck can also induce dry mouth, which may seriously compromise oral health. Incorporating diligent oral hygiene and preventive treatment, this program alleviated, and in some cases eliminated, many of the unpleasant oral health problems that cancer patients suffer.

#### **Acquired Immune Deficiency Syndrome**

Oral infections have taken on special significance in dental research with the advent of acquired immune deficiency syndrome (AIDS). NIDR grantees have found growing evidence that the oral cavity is a frequent site of the serious opportunistic infections and of the Kaposi's sarcoma associated with AIDS. Moreover, the need to treat oral conditions in AIDS patients and to adopt measures to ensure that both dental personnel and the general public are protected against exposure to the AIDS virus is imperative.

Several NIDR-supported investigators have now identified specific oral lesions that may precede the clinical picture of AIDS. Recent studies confirmed that the unusual oral lesion, hairy leukoplakia, is one of the clinical

markers for the later development of AIDS in many patients. This new finding underscores the importance of regular examinations for oral tissue changes in high-risk groups, and the need for dental professionals to be alert to the possible presence of oral lesions in their patients.

#### **Herpes Vaccine**

An experimental herpes vaccine that not only counters an immediate herpes attack but also prevents the virus from establishing a latent, recurrent infection was developed last year by a team of researchers from the NIDR and the National Institute of Allergy and Infectious Diseases. The vaccine, which has been tested successfully in laboratory mice, is targeted against herpes simplex virus type 1 (HSV 1), the organism responsible for oral cold sores. The vaccine also appears to provide substantial protection against HSV 2, the cause of genital herpes. Now, 1 year later, the scientists have shown that the vaccine continues to provide immunity in the animals. This is the first demonstration of the duration of effectiveness of an experimental herpes vaccine, and gives further impetus to animal testing in anticipation of human trials.



*In studies with mice, NIDR researchers have developed a vaccine that appears to offer substantial protection against herpes simplex type 1 and 2.*

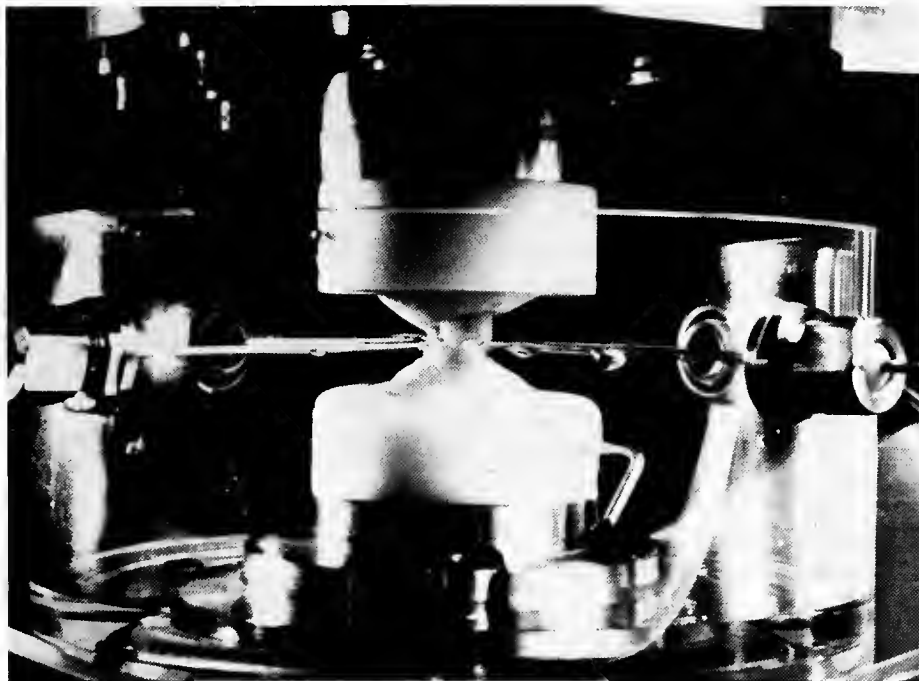
#### **Restorative Materials**

While progress toward disease prevention continues, the need remains to provide safe, effective, and reliable treatment for the millions of people who suffer from the broad range of dental disorders. The dentist's stock-in-trade of restorative materials has expanded to include new and stronger amalgams and tooth-colored composite materials—mixtures of glass and plastic particles. A 2-year study by NIDR-supported scientists has shown that composites compare favorably with amalgams in filling cavities in children's primary molars because they need only last for as long as the child retains the tooth. Composites placed in permanent molars, however, are less successful due to weakening from prolonged hard wear and the subsequent risk of recurrent decay. In response to research recommendations outlined in the Institute's Long-Range Research Plan, current studies are focused on improving the durability of composites for long-term restoration of all teeth in both children and adults.

#### **Artificial Mouth**

The development of new and better dental materials may come more quickly now, thanks to a biomechanical system that simulates both the chewing motion and environmental conditions in the human mouth. This unique device, designed by NIDR grantees, would have a major impact on dental research and treatment by expediting the evaluation of new materials for use in dental practice.

Time effectiveness is a significant feature of this system, called ART by its developers. An acronym for Artificial Resynthesis Technology, ART can subject dental materials or restoration techniques to the equivalent of 5 years of wear in just a few weeks. This considerable time savings in the development of new products can reduce the cost of research, decrease the time required for the transfer of new technologies from the laboratory to the operatory, and ultimately decrease the cost to the patient.



*While the mechanical mouth developed by NIDR grantees at the University of Minnesota School of Dentistry looks nothing like the real thing, it simulates the environment and chewing activity of a real mouth.*

### **Mussel Glue**

Findings from a decade of research supported by NIDR are about to directly benefit dentistry, medicine, and industry. A remarkable adhesive protein has been isolated from mussels and reproduced. This rapid-acting "superglue" anchors the mollusks to virtually any underwater surface, including rock, metal, glass, wood — even to another shellfish—and holds potential for a broad range of practical applications.

In dentistry, for example, the protein adhesive could be used as a decay-preventing sealant or to repair dental caries by gluing fillings into teeth. It may also have properties superior to dental cements currently available for cosmetic applications such as securing crowns and bridges and repairing fractured teeth. In addition, mussel glue has a potential role in periodontal surgery to aid the healing process by creating a strong bond between gum tissue and teeth. It is expected that the adhesive will be available for feasibility studies of dental uses within 2 years.

Possible medical applications are equally exciting, particularly in the

field of orthopedics for the repair of broken bones. In industry, demand is great for an adhesive that can be applied underwater. The Navy and nearly a dozen major companies have expressed interest in this material for such potential applications as ship repairs and protection from corrosion and marine fouling, and for a number of diverse industrial uses. Scientists are now exploring recombinant DNA technology to produce the protein in large quantities.

### **Mineralized Tissues**

In the past 2 years, we have seen major gains in mineralized tissue research. Earlier studies of bones and teeth have paid off in important discoveries concerning collagen, tooth enamel, and factors that regulate the growth, maintenance, and repair of the body's hard tissues. With these findings has come increased understanding of the destructive processes seen in the broad range of bone diseases. This vital, basic information is leading to new therapies for systemic disorders as well as new approaches to diagnosis and treatment of dental diseases.

### **A Closer Look at Bone**

For the first time, NIDR scientists have perfected cell culture techniques that permit long-term studies of the behavior of normal and diseased bone cells in a laboratory dish. The investigators are studying cells from patients with a variety of bone disorders, from the hereditary "brittle bone" diseases like osteogenesis imperfecta, to the crippling diseases that affect so many older Americans—osteoarthritis and osteoporosis.

These researchers have also cloned the genes that code for two important proteins, osteonectin and bone proteoglycan, involved in bone metabolism. The investigators are using monoclonal antibodies to compare thinning osteoporotic bone tissue with normal tissue in search of clues to this disease process.

### **Osteogenin**

Another exciting development has been the isolation and purification of a small protein, called osteogenin, believed to be an active factor inducing new bone formation following bone fracture or loss. Plans now call for an NIDR-industry collaborative effort to characterize the protein fully, with the hope of using recombinant DNA techniques to produce osteogenin in quantity for use in reconstructive surgery.

### **Tooth Enamel Gene**

Using genetic engineering techniques, NIDR grantees have for the first time identified and cloned the gene for one of the four protein components of tooth enamel. Their work, which was carried out in mice, has also resulted in decoding the genetic instructions for the protein, called amelogenin.

These findings could provide important clues to determining the role of amelogenin in the formation of the primary mineral component of teeth. Moreover, as the investigators learn more about the molecular processes involved in the formation of normal tooth enamel, they are applying this information toward a better understanding of what goes wrong in disorders such as



amelogenesis imperfecta, a hereditary disorder of faulty enamel development. Significantly, these findings extend beyond the boundaries of tooth formation to the fundamental process of gene regulation that dictates the development of all tissues—both normal and defective—in animals and man.

## **Congenital and Acquired Craniofacial Malformations**

NIDR-supported scientists have made important research contributions to the field of craniofacial anomalies through genetic and cell biology studies of the various hereditary defects that involve the face and head. The most common of these disorders are cleft lip and palate. Scientists believe that these and other structural abnormalities of the jaw and facial bones are caused by a combination of genetic and environmental factors. Although recent advances have made it possible to correct many of the defects, determining the proper timing of the surgery has posed problems for clinicians.

### **Corrective Surgery**

NIDR grantees now report that surgery in children as young as 3 months of age can prevent hearing loss caused by otitis media, middle ear disease common in cleft palate patients. Related research completed in 1985 also suggests that corrective craniofacial surgery in patients as young as 1 or 2 years old is safe and does not undermine normal facial growth. Studies of children who had had early surgical intervention showed normal appearance by young adulthood, a factor which softened the spectre of social adjustment problems and learning disabilities often found among cleft palate patients.

### **Neural Tube Defects**

NIDR-supported studies are helping scientists understand how certain types of birth defects—malformations of the neural tube—occur. These abnormalities, in which a portion of the spinal cord or brain remains exposed at birth, begin in the early weeks after conception.

In one or two of every 1,000 live births, the vital process of neural

tube formation goes awry. This rate is markedly increased among mothers who are exposed to certain chemical agents such as sodium valproate, an anticonvulsant used to control epilepsy, during this critical stage of early embryo development. Laboratory studies now reveal that sodium valproate significantly delays the closing of the neural folds that form the tube. Such delays can even prevent closure altogether by disrupting the delicate process of tissue growth and development in which exact timing is critical. These findings not only signal progress in our understanding of neural tube defects, but also may provide valuable insight into the early, critical days and weeks of embryonic development.

### **New Reconstructive Material**

NIDR grantees have developed a new restorative material, chlorinated polyethylene, that can be used to construct artificial replacements for portions of the face and jaw damaged by injury or disease. The new substance not only has improved molding and elastic properties, but also can be permanently custom-colored to match a person's facial complexion. This advance offers hope to thousands of people who suffer from the physical and psychological pain of facial disfigurement caused by tumors, birth defects, infections and other diseases, and accidents.

## **Salivary Glands and Secretions**

Human salivary glands secrete about a quart of saliva a day. Made up of water and over 30 other components, this natural liquid protects, maintains, and even repairs oral tissues. In the past 2 years, NIDR investigators solved the puzzle of how water and salt are taken up by salivary cells and how the fluid, along with other ingredients, is later secreted in the form of saliva. These discoveries have led to new classifications of patients who suffer the painful symptoms of dry mouth, a condition that predisposes to a variety of oral infections, including tooth decay and gum disease.



*Clinical researchers studying xerostomia, or dry mouth, have developed treatments to stimulate saliva production in patients with salivary gland disorders. Here, saliva samples are collected to measure the effectiveness of an experimental drug.*

These individuals represent a surprisingly large group that includes people with specific glandular and rheumatological disorders, patients who have undergone radiation and chemotherapy for cancer, and many adults who take daily medications with a side effect of oral dryness. Tests developed by NIDR scientists show that in some of these people, the salivary cells are able to take up salt and water but are blocked in secreting the end product, saliva. That observation has led to the experimental use of the drug pilocarpine, which has proven to be a safe and effective means of unblocking the secretory channels and restoring the flow of saliva.

## **Behavioral Research**

Fear and apprehension prevent an estimated 6 to 16 percent of Americans from seeking dental care. Others visit the dentist, but their excessive anxiety complicates treatment, establishing a vicious circle that reinforces their notions that dental treatment is difficult and painful.

### **A Dental Phobia Program**

Behavioral researchers supported by NIDR are exploring a variety of non-pharmacological approaches for overcoming dental phobia. One group of grantees has developed a videotaped fear-reduction program aimed at motivating people to visit a dentist. The half-hour program includes information about dental fear

and instructs viewers in coping skills and relaxation techniques for overcoming their anxiety.

Preliminary tests have shown that the videotaped program is successful in motivating moderately fearful people to visit a dentist. Not unexpectedly, it has little effect on highly fearful people who avoid dental treatment. The researchers conclude that a taped fear-reduction program, which could be shown to groups or even to entire communities through television, would make the benefits of behavioral therapy available to many people at a reasonable cost.

### **School-Based Fluoride Programs**

NIDR contractors have surveyed a sample of public school districts in the United States to identify the factors that predict whether a school district will adopt fluoride mouth rinse programs and whether the programs will continue to be implemented several years later. They have found that school superintendents who do adopt fluoride programs usually learned of them through local or regional public health officials rather than through other educators or written documents. The survey results also show that rural school districts and those with a higher percentage of students from low-income families were more likely to offer fluoride programs.

### **Preventive Behaviors**

Several groups of NIDR grantees are studying preventive behaviors related to periodontal disease. They are examining the frequency and effectiveness of toothbrushing and flossing among study subjects, and are developing interventions designed to improve the reliability and efficiency of these preventive behaviors. Results to-date show that a person's oral health knowledge and skill has very little correlation with how often he or she brushes and flosses. There is a high correlation, however, between how often a person brushes and flosses and the frequency of those behaviors among the person's significant others, such as spouses or roommates.

### **Behavior and Disease**

Behavioral research at the Dental Institute focuses not only on strategies for promoting oral health, but also on the behavioral contributors to oral disease. Studies have linked alcohol use to tooth grinding—a habit that can have disastrous consequences in terms of tooth wear and pain. Use of chewing tobacco, which is becoming increasingly popular in the United States, can lead to oral cancer. Stress has been implicated in a variety of oral problems, including canker sores, cold sores, tooth grinding, and certain orofacial pain syndromes.

### **Implantology**

After a slow beginning, implantology research is now moving ahead. Infection remains the primary cause of implant failure, but investigators are learning more about specific procedures and patient characteristics that are conducive to implant survival. Several major criteria that are improving the success rate have emerged. These criteria include (1) selecting patients with adequate bone structure to hold an implant, (2) choosing the proper implant device, (3) allowing sufficient time for gum and bone tissue to heal around the implant before attaching a prosthesis, (4) avoiding excessive stress on the implant, and (5) following a program of regular care of the implant, the attachments and the surrounding tissue.

An Institute-supported, long-term clinical trial seeks to determine the efficacy and safety of blade implant-supported bridges as compared to traditional cantilever bridges, and to develop a clearer understanding of implant acceptability, disease activity, and the mechanism of implant failure. Final results of the trial, now at the halfway mark, will be available at the conclusion of the 5-year study.

Implantology research maintains its primary emphasis on improving existing materials, designs, and technology. These studies will continue to focus on factors that influence implant acceptance or rejection, and the development of more specific criteria and models to predict implant performance.

### **Pulp Biology**

Deep within the center of the tooth, protected by the hard layers of dentin and enamel, is a soft tissue called the tooth pulp. The pulp is the living part of the tooth. Its blood vessels nurture, repair, and renew the surrounding hard tissue. Nerves in the pulp monitor the tooth's environment, sounding the alert in case of injury.

Because it is so small and located so deep inside the tooth, pulp has been a difficult tissue to study. Now, however, new techniques are enabling scientists to study the pulp microscopically in animals, observing blood flow under normal conditions and in response to tissue insults. The investigators are examining the ultrastructural details of pulp cells, and are analyzing the biochemical factors involved in control of pulpal blood flow and tissue response to damage.

The results of these new studies offer hope for better treatment and prevention of damage to the tooth pulp. Currently, pulp disorders affect millions of people each year, giving rise to severe pain, abscesses, cysts, and all too often leading to a root canal and the loss of tooth vitality or to loss of the tooth itself. There is also the danger that microorganisms invading the pulp may spread to other parts of the body and result in such conditions as endocarditis—infection of the membrane lining the heart.

### **Nutrition**

What we eat, and do not eat, has both direct and indirect consequences for our oral health. The clearest association between diet and oral health is that between consumption of sugar and other highly fermented foods and development of dental caries. Sugar alone does not cause tooth decay, but certain bacteria in the mouth use sugar to produce acids that dissolve tooth enamel, producing decay.

This year, NIDR grantees reported that addition of fluoride to sugar in the diet can significantly reduce the incidence of decay on smooth surfaces of teeth. The investigators added small amounts of fluoride to



sugar in the diets of laboratory rats, and compared those rats to another group fed nonfluoridated sugar. The results showed that animals fed fluoridated sugar developed far fewer cavities.

Though fluoride is added to drinking water in many parts of the United States, it is not currently added to foods. In Britain, however, chewable sugar tablets containing fluoride are available, and fluoridated salt is used extensively in Hungary and Switzerland. Sugar may be an ideal vehicle for fluoride administration, because fluoride appears to be most effective against caries when it is present at the time acid attacks the tooth enamel.

### Science Transfer

The tremendous growth in the oral health sciences has spurred development of effective ways to collect, process, and disseminate NIDR's ever-increasing body of knowledge. To maximize the benefits of dental research, trends, results, and practical applications must be communicated rapidly and accurately to other researchers, practitioners, the media, and the public. The transfer of scientific information is a key element central to the success of NIDR's basic and clinical research programs.

In FY 1985 and 1986, NIDR brought its research advances to the public and the scientific community through a variety of vehicles. *NIDR Research Digest* highlights recent accomplishments and is included in the newsletter of the American Association for Dental Research. In addition, a special NIDR research page now appears bimonthly in the *Journal of the American Dental Association*, and NIDR research advances are often highlighted in NIH's column in the *Journal of the American Medical Association*.

Another key outlet for research information is the lay press. Working closely with the print and electronic media, the Institute has placed stories and interviews involving scientific advances in virtually every major national magazine and newspaper, and radio and television network.



*Pictured are two scenes from the joint ADA-NIDR television public service announcement which emphasize the protective benefits of sealants.*

The Institute has introduced a new computer program, NIDR ONLINE, that provides access to the latest news about NIDR research and development activities, and lists conference schedules, a variety of directories, announcements or requests for grant proposals, and

related information. The system also stores listings of NIDR publications and provides a means of ordering them directly through the computer's message bank. The Institute developed this free service to help dental libraries speed up the science transfer process.

During the past 2 years, the Institute produced three films in col-

laboration with private industry: "Prescription for Periodontal Health" "Fantastic Fluoride," and "Fluoride: The Magnificent Mineral." The latter has been prepared for viewing by the hearing impaired, and both fluoride films are being translated into several foreign languages. NIDR also prepared user guides for both fluoride films. Together, the films have been seen by more than 242,000 viewers. In addition, a 30-second television public service announcement on sealants was distributed and used by all major networks. Exhibits are now being prepared on fluorides and sealants for use at health fairs, libraries, shopping malls, health departments, PTAs, and dental and dental hygiene schools.

The results of recent NIDR-supported studies have established a pathological relationship between periodontal disease and diabetes mellitus. With early diagnosis and prompt treatment, however, oral health—and diabetic control—can be maintained. This is the message of a new exhibit designed in FY 1986 to inform the medical, dental, and diabetes communities about this major complication. The exhibit also coordinates with a new NIDR diabetes-targeted publication developed in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases. Titled "Detection and Prevention of Periodontal Disease in Diabetes," the booklet is a basic, informative guide for primary care physicians and allied health professionals who work with diabetes patients.

### Conferences and Workshops

In February 1985, the Institute—for the first time in its history—invited the deans of all North American dental schools to a special meeting at the NIH campus. The NIDR-University Partnership Conference explored how the Institute can be more responsive in fostering dental research in a broader range of higher learning institutions. The workshop provided attendees an opportunity to exchange ideas on how NIDR research support should be allocated, how to enhance the research capacity of dental schools,

and how NIDR and universities can work together to meet the needs of the entire scientific community.

A workshop on Dental Plaque Control Measures and Oral Hygiene Practices also took place in February 1985. The meeting enabled participants to review the state of scientific knowledge in this area and to identify research needs and opportunities. Workshop information and recommendations were published in an official conference proceedings.

In the spring of 1985, the Institute sponsored a consensus development conference at NIH on Anesthesia and Sedation in the Dental Office. Participants shared important study results and issued recommendations for strengthening anesthesia practices, training, and research.

In September 1985, NIDR sponsored a workshop on pain and anxiety control with a focus on Integrating Pharmacological and Behavioral Therapeutic Modalities and Research Methodologies. Experts in this aspect of the behavioral sciences convened in Bethesda to discuss current treatment strategies in the context of research needs.

NIDR actively encourages research in the area of biocompatibility of metals, including dental amalgam filling materials. In FY 1985, the Institute convened a special meeting of mercury experts to once again review the progress of research in this area. Participants represented eight major Federal agencies whose mission involves mercury research.

A task force meeting concerning AIDS and Oral Pathology was called by NIDR in November 1985 to clarify the direction and scope of needed research involving AIDS and the oral cavity. The session focused on the effects of the AIDS virus on the immune system; the clinical manifestations of the disease and associated opportunistic infections; and on the treatment, transmission, and epidemiology of AIDS. The task force proposed a list of recommendations for NIDR in leading and sponsoring research in this field.

Experts gathered in Bethesda in January 1986 to discuss the future direction of anticaries vaccine

research. Participants examined the current status of the vaccine's development and urged NIDR to continue studies of the cause of dental caries, to define the most effective immunogen, and to learn more about immune responses to such a vaccine.

The use of chewing tobacco and snuff is increasing at alarming rates, particularly among young people. A consensus conference held in FY 1986 on Health Implications of Smokeless Tobacco explored the types of smokeless tobacco products, history and current patterns of use, constituents, and health and behavior effects. The panel concluded that the use of these products is a health-endangering behavior that holds clear potential for serious, long-term consequences.

A consensus conference sponsored by NIDR in May 1986, Integrated Approaches to Management of Pain, featured discussions of pharmacological agents as well as non-pharmacological interventions and how these approaches can be used together. The participants also emphasized the achievements and potential of nursing as they contribute to the overall effort of the health care team.

NIDR sponsored a conference on Evaluation and Management of Salivary Gland Dysfunction in May 1986. Participants reviewed state-of-the-art knowledge on the problems associated with secretory dysfunctions, including the assessment and treatment of these disorders. The conference provided valuable information to both researchers and practitioners.

A conference on Microbiological Diagnosis in Dental Caries and Periodontal Disease was sponsored by NIDR in June 1986. Participants at the conference assessed current methods for sampling, identifying, and quantifying the microorganisms associated with caries and the periodontal diseases.

### Plans and Prospects

Prevention is the theme that will dominate NIDR research activities as the Institute moves into the nineties. The sharp reductions in the

prevalence of dental caries in schoolchildren over the last generation are dramatic evidence that prevention works. Prevention also is paying off in terms of reducing the Nation's dental bill. Department of Commerce figures report that dental expenditures for personal dental services in 1984 were \$19.8 billion. The preliminary figure for 1985 is \$21 billion. These totals represent substantial declines in the rate of growth of dental care expenses—declines that have resulted from the adoption of community water fluoridation, other systemic and topical fluorides, and better oral hygiene habits, as well as the provision of preventive services by dental practitioners. Had the growth rate not slowed, the Nation's dental bill for 1985 alone would have been almost \$5 billion more—even after adjustment for inflation.

What dental research has achieved in terms of improving the oral health of children is only the prelude to what NIDR hopes to accomplish in the years ahead. No one—child, teenager, young adult, or mature American—need ever lose a tooth to disease. To realize that goal the Institute is expanding research to look at all aspects of normal and abnormal oral tissue growth, development, maintenance, and repair; to develop safe, easy-to-use agents and techniques for professional and self-care; and to ensure that the messages coming from the laboratory are well heard by the profession and the public. The range of oral diseases and conditions studied is growing and as the findings and intellectual foundations for dental science deepen, so will the scope and skills of the dental practitioner.

The dental caries story is by no means over. Next year the Institute will conduct a nationwide survey of the oral health of schoolchildren to parallel the 1979-80 NIDR study which showed the dramatic declines in decay that had been achieved over the previous decade. The repeat survey is needed to determine if the caries reductions are being maintained. In addition, the examiners will note the presence of other oral conditions in children,

such as gingivitis and soft tissue lesions. The Institute will continue to promote the adoption of new or improved caries-preventive measures. These include the use of fluoride dentifrices, mouth rinses, tablets and other fluoride vehicles, as well as applications of dental sealants to prevent decay on the rough surfaces of children's teeth—the areas least affected by fluoride. Authorities consider that the combined use of fluorides and sealants could virtually eliminate decay affecting the crowns of teeth (coronal caries) in schoolchildren in the years ahead. Greater attention will be paid to tailoring prevention to high-risk groups, making use of miniaturized devices that can be attached to individual teeth for the slow release of fluoride or antimicrobial agents.

#### **Oral Immunity**

Even with the powerful means of caries prevention now available, there are practical realities to consider. Only an estimated 60 percent of the U.S. population sees a dentist in any year; only 53 percent of Americans enjoy the benefits of community water fluoridation. Future NIDR oral health promotion and disease prevention activities are planned to boost those percentages through community-based demonstration research projects, and other science transfer activities. These efforts should act synergistically with what is already happening in the United States: Americans are showing increased interest and concern about health and well-being; they read more, they know more, and they are doing more to improve general health and fitness. At the same time, the Institute will expand basic studies of oral immunity and oral ecology in the expectation that such research will yield powerful new means of preventing oral diseases—not only dental caries, but also many other painful and costly conditions.

#### **Caries Immune Studies**

A safe and effective vaccine that could be given in infancy to prevent caries from ever developing in children would be an alternative

solution to caries prevention, particularly among groups with limited access to dental care. Many approaches have been tried with varied degrees of success. Now that the techniques of biotechnology are available to isolate and generate antigens of high purity, it is possible to list the hypothesis that the oral presentation of purified *S. mutans* antigens early in life would stimulate an immune response from lymphoid tissue developing in the lining of the gut. Later in infancy when the teeth erupt—a time when they are most vulnerable to colonization and attack by *S. mutans* bacteria—the now-educated immune system would mount a strong antibody response to inhibit or delay bacterial colonization.

#### **Herpes Vaccine Studies**

Two methods of developing immunity to infection by the herpes simplex type 1 virus (HSV 1) have shown promise and will continue to be explored. One method described earlier uses the vaccinia virus as a vehicle for an HSV 1 gene that codes for an important surface protein of the herpes virus, glycoprotein D. This vaccine has been shown to be effective in preventing primary and latent infection by HSV 1, which is associated with oral herpes, and provides substantial protection against HSV 2, which is associated with genital herpes. Mice vaccinated over a year ago are still immune to infection, encouraging further testing of the experimental vaccine, possibly through the use of adjuvants and booster shots. An alternative herpes vaccine is under development by a grantee who will attempt to synthesize an important subunit of glycoprotein D and use this molecule as the immunizing agent. If effective, such an approach would avoid issues concerning the reintroduction into the population of the vaccinia virus (formerly used to immunize against smallpox).

#### **AIDS Immune Studies**

The NIDR is expanding research on the natural history of infection by the HTLV III/LAV agent, the cause of AIDS. Normally, the oral cavity serves as a major barrier to infection

by virtue of specific immune factors and cells (e.g., secretory immunoglobulins, monocytes) and nonspecific antibacterial factors such as certain proteins found in saliva (e.g., lactoferrin, lactoperoxidase). A group of histidine-rich proteins, also present in saliva, provide antifungal protection. In addition, saliva cleanses the oral cavity of bacteria through swallowing. Because the AIDS virus kills or weakens important immune cells and functions, AIDS patients frequently develop oral opportunistic infections which can then spread systemically. Some report dry mouth or develop unique oral lesions as well. Thus, studies of oral tissue changes in risk groups, in individuals who are carriers of the virus or of AIDS antibodies, or in patients with frank AIDS, provide an unequalled opportunity to study the immunosuppressive effects on the body's main entryway of a devastating "experiment of nature."

Future AIDS studies will continue to build on current immunologic research which has disclosed a number of defects in monocytes and B lymphocytes. Interventions to restore immune capacity, to eliminate the AIDS virus, and to treat oral opportunistic infections, dental diseases, and other signs and symptoms associated with AIDS, are also planned. These include therapies for the chronic pain some AIDS patients develop, presumably because of nervous system injury. Several of these clinical studies are being undertaken in collaboration with other NIH components.

The NIDR also plans to join with the U.S. Army/Walter Reed in an interagency agreement to take part in comprehensive longitudinal studies following risk groups and AIDS patients in military populations. Collaborative studies with the Veterans Administration also may be conducted, following veteran populations with AIDS. The Institute is also cooperating with other concerned public and private agencies to enhance understanding of AIDS among the public and health professionals and to promote the adoption

of appropriate disease prevention methods applicable to any infectious disease which might be encountered in dental settings.

### **Immunity in Periodontal Diseases**

Prevention of the periodontal diseases is now possible, thanks to the discoveries about the cause and natural history of these diseases. The periodontal diseases, like dental caries, are associated with bacteria in plaque that builds up on teeth and surrounding tissue. In addition to the direct tissue-destroying activities of the periodontally destructive bacteria, research has revealed that dysfunctional immune responses can exacerbate the symptoms and severity of these diseases. Now, the study of two relatively rare periodontal diseases, prepubertal and juvenile periodontitis, has added a genetic component. It appears that these rapidly destructive forms of periodontal diseases are associated with specific inherited defects in certain white blood cells, polymorphonuclear leukocytes (also known as neutrophils). These defects are thought to account for the severity of these diseases in the young people affected.

The way is now open for NIDR to direct detailed genetic studies of these forms of periodontal disease, making use of such techniques as restriction fragment length polymorphisms to discover which chromosomes carry the defective gene or genes and to develop genetic markers which would enable investigators to identify those individuals in an affected family who are at risk. Furthermore, the use of these genetic mapping and linkage techniques can be expected to enhance understanding of other diseases as well. For example, a variety of connective tissue diseases such as rheumatoid arthritis involve dysfunctional immune responses. Knowledge of the variety and location of human genes governing major immune cell functions could lead to better understanding and treatment for rheumatoid arthritis and other progressive degenerative diseases affecting connective tissue and bone.

### **Periodontal Diseases Prevention**

Meanwhile, the NIDR will continue to promote the adoption of appropriate oral hygiene to prevent the most common form of periodontal disease, chronic periodontitis in adults. The critical point is that chronic periodontitis always begins with gingivitis and gingivitis can be reversed by appropriate mechanical methods of removing plaque, such as thorough toothbrushing and flossing. Thus the prevention of gingivitis effectively prevents periodontitis. The NIDR anticipates that new, safe antimicrobials will become available in the future. These chemical agents, incorporated into mouth rinses, could be prescribed by dentists for use by patients who cannot effectively perform mechanical oral hygiene or who have developed early, reversible stages of periodontal disease. More advanced cases, where pockets have formed around affected teeth, require professional care.

The NIDR has developed educational films, pamphlets, and other media approaches to enlighten the public on the periodontal diseases and means of prevention. In addition, community intervention studies are being planned for the prevention and control of periodontal diseases in adults.

### **Epidemiology**

One of the most important undertakings of the NIDR in the past 2 years has been the Epidemiologic Survey of Oral Health in Adults. In the first phase, which was completed in January 1986, five teams of investigators visited 600 worksites and 200 centers for the elderly throughout the country and collected oral health data from more than 20,000 people aged 16 to 75 years and older. Preliminary findings concerning the prevalence of coronal, secondary, and root caries; the periodontal diseases; edentulousness; and other oral conditions will be announced later this year. These analyses will provide benchmarks against which to measure changes and improvements in the oral health of adult Americans over time, and



*The NIDR is conducting a nationwide survey to determine the prevalence of periodontal diseases, as well as caries, in the adult population — an important step in planning prevention strategies. Teams of dentists have examined 20,000 people age 16 to 75 at various worksites and senior centers around the country.*

guidelines for the planning of practical research, prevention, and treatment programs targeted to specific problems and populations.

The Institute particularly encourages research to elucidate what happens to oral tissues and fluids in the normal course of aging, both in relation to other normally occurring changes in the body and in the presence of disease. A new Research Agenda on Oral Health in the Elderly has been developed in collaboration with the National Institute on Aging (NIA) and the Veterans Administration (VA). The agenda was designed to alert the research community and the general public to the need for expanded research in these areas. The NIDR expects to collaborate with the NIA and the VA in studies that can make use of the unique resources and personnel that each agency represents. One outcome of this collaboration that has already occurred is the reinstitution of an oral health component in NIA's Baltimore Longitudinal Study.

### Biotechnology

Few scientists anticipated the rate at which recombinant DNA and monoclonal antibody techniques would spread throughout the Nation's biomedical research laboratories. Today, virtually every NIDR intramural laboratory makes use of genetic probes, hybridomas, and other associated skills and techniques of biotechnology. These methods are accelerating the rate of progress from basic research to clinical application. They also are stimulating interest on the part of the private sector, which sees the commercial potential for the products or processes derived from biotechnology. The NIDR invited private sector representatives to a meeting in May 1986 to hear presentations by staff scientists and to discuss the potential for collaborative efforts. Among some of the developments discussed were:

- The production of a high transformation system for introducing novel genes into *Lactobacillus casei*, a common bacterium found in foods. Potential applications discussed were the introduction of

flavor enhancer and spoilage resistance factors into the bacterium. It might also be possible to incorporate detoxifying and antitumor agents into lactobacilli strains that normally colonize the intestinal tract.

- A new assay to aid in staging tumor cells and to test antimetastatic agents. The assay is based on the development of a reconstituted basement membrane material which would be used as a substrate for culturing biopsied cells from human tumors. This material has also been used experimentally to promote nerve regeneration.

- The potential applications of a small protein, osteogenin, which has been isolated and purified from bone matrix, for use as a bone growth-inducing factor in case of bone fracture or loss.

- A new adhesive which has been derived from the natural secretions marine mussels use to attach to hard surfaces under water. This would be the first man-made glue that could be applied effectively in a wet saline environment — the normal surround of human tissues — and hence of enormous value in dentistry and medicine as well as in shipbuilding and maintenance.

### Issues and Policies

The invitation to industry to hear findings emerging from the research of NIDR staff scientists and grantees is part of the Institute's policy as expressed in the NIDR Long-Range Research Plan, *Challenges for the Eighties*. The NIDR recognized that it would be increasingly important to the Institute's mission to forge deeper links not only within the traditional segments of the dental research community, the dental schools, and dental practitioners, but also with the private sector and the general public. Part of the rationale for this enhanced "outreach" derives from awareness that all government agencies share in the need to constrain spending to lower the Federal deficit. At the same time, the NIH itself has altered the rules and regulations governing private sector/government laboratory collaborations. Thus, new opportunities have



been created which can strengthen the research arm of the NIDR and facilitate commercial development and applications of research that can enhance public health.

Some of the ways that private sector/NIDR collaboration might occur have been discussed in terms of support of staff fellowships or research training programs. Such programs could have an immediate as well as long-range payoff. They would encourage talented young people still in college or in preparation for the health professions to consider careers in research and thus help turn the tide toward research careers in science. And they would ensure that an adequate supply of well-trained researchers would be available to carry on the job of science in the years to come.

The NIDR has been aware of the need to enlarge the pool of researchers in oral health, especially clinical investigators. It was for this reason that the Institute launched the Dentist-Scientist Award and the Physician-Scientist Award for Dentists in 1985. These unique 5-year career development programs provide D.D.S. or D.M.D. degree holders with a combination of postgraduate specialty training, studies equivalent to a doctorate in a biomedical field, and research experience guided by mentors. These programs have been well received by the research community and there are now some 50 candidates in place in either individual or institutional programs. If expansion of these programs can continue as originally planned, there would be 150 new clinical investigators to add to the research pool by 1990.

The addition of these new clinical investigators will need to be supplemented by expansions in other career development and research training programs to meet the totals projected in the Institute of Medicine 1985 *Report on Personnel Needs and Training for Biomedical and Behavioral Research*.

### **Continuity and Balance**

It is not only a question of assuring an adequate supply of talented minds to provide the continuity in research from generation to genera-

tion that is so essential to progress, but it also is a question of providing adequate resources and research environments. The NIDR needs to employ all the mechanisms of support available at the NIH. In particular, the ad hoc advisory panel, which advised the NIDR on its use of centers and other large grant mechanisms, recommended that the Institute continue to support, under open competition and rigorous peer review, centers that would conduct broad multidisciplinary research. Accordingly, the Institute issued a Request for Applications (RFA) for new Research Centers for Oral Biology. This RFA has been well received in the dental research community, and the Institute anticipates receiving perhaps 20 applications by the closing date, December 1, 1986. The ad hoc panel also recommended the implementation of a core center program. Core grants enable several grantees in a research facility to share resources and equipment. The NIDR was also encouraged to expand categorical and thematic centers and has identified important areas that could benefit from the perspectives and resources available at a center: Oral Soft Tissue Diseases and Neoplasms, Oral Ecology, Gerodontics Research, and Biomaterials Science.

The establishment of centers and other major research support mechanisms does more than supply funding for a group of investigators and projects. These programs create a focus for a problem or research area that can act as a magnet to attract other investigators and generate greater awareness on the part of the public and the profession. Further, they provide opportunities for research training and facilitate the movement of basic research to clinical applications. Thus, centers frequently initiate clinical studies, or cooperate in collaborative controlled clinical trials.

Not all research in the biomedical disciplines is ready for the focused approach of centers. The NIDR, in parallel with all other NIH components, allots the lion's share of its budget to the support of individual

investigators who are inspired by their own ingenuity and interests and want to put a hypothesis to the test. Such investigators are the mainstay of biomedical and behavioral research, exploring new ideas and fueling the engine of progress. They are especially important today when dental science is in ferment, when those in the field share the excitement and stimulation that permeates all biomedical and behavioral research. The NIDR has done much to encourage that excitement, sometimes pointing to areas of need, sometimes discouraging further research in well-plowed fields. In this way the Institute strives to achieve balance in the research portfolio, a balance that is designed to maximize the yield from its research resources and speed the fruits of research for the benefit of the American public.

# The Biennial Report of the Director, National Institute of Diabetes and Digestive and Kidney Diseases

## History

The following events represent milestones in the development of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

- August 15, 1950—The National Institute of Arthritis and Metabolic Diseases was established through the Omnibus Medical Research Act (P.L. 81-692).

- 1959—Dr. Arthur Kornberg, former chief of the Institute's Enzyme and Metabolism Section, won the Nobel Prize for his work synthesizing nucleic acids.

- May 19, 1972—The name of the Institute was changed to the National Institute of Arthritis, Metabolism and Digestive Diseases (Public Law 92-305).

- 1972—Dr. Chris Anfinsen, former chief of the Institute's Laboratory of Chemical Biology, won the Nobel Prize for his work on the primary sequence of amino acids in proteins.

- December 17, 1980—The NIAMD became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (Public Law 96-538).

- April 1982—The Institute was designated a Bureau of the NIH and the program clusters were elevated to Division status, creating four extramural Divisions and the Division of Intramural Research.

- 1985—The Health Research Extension Act of 1985 (Public Law 99-158) divided the programs of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases into two separate Institutes: the National Institute of Diabetes and Digestive and Kidney Diseases, whose programs are the focus of the present report; and the new National Institute of Arthritis and Musculoskeletal and Skin Diseases, for which a separate report is provided.



*NIDDK-supported research has led to promising new developments in conditions such as diabetic neuropathy, gallstones, and hereditary anemias.*

- 1985—Dr. Pierre Renault was designated Acting Director, National Institute of Diabetes and Digestive and Kidney Diseases.

## Introduction

The NIDDK conducts and supports research on many of the most serious diseases affecting the public health. The Institute's mission includes both basic and clinical research on these diseases, among which are diabetes, endocrine and metabolic disorders including cystic fibrosis; digestive diseases and nutritional disorders; and kidney

and urinary tract diseases and blood disorders. Basic research is conducted and supported in such areas as endocrinology, genetics, metabolism, biochemistry, physiology, molecular biology, pathology, and pharmacology.

The Institute supports basic and clinical research through investigator-initiated grants, program project and center grants, and career development and training awards. In addition, it supports research and development projects and large-scale clinical trials through grants, contracts, and cooperative agreements. The Institute's Division of Intramural Research conducts basic studies in



endocrinology; genetics; chemistry; biochemistry; metabolism; physical, chemical, and molecular biology; chemical physics; pharmacology; and pathology. Its scientists also conduct clinical research on diabetes, other metabolic diseases, cystic fibrosis, endocrine disorders, digestive diseases, kidney diseases, and blood disorders.

The focus on basic research that has traditionally guided NIDDK's programs is grounded in the fact that a fundamental understanding of the intrinsic nature of each disease is imperative for the development of effective strategies for prevention and therapy—and the work of the Institute involves many chronic and progressive diseases with as-yet-unknown etiologies. Advances in basic knowledge are continually and productively expanded into appropriate clinical studies and trials, and into programs of technology transfer and information dissemination to the community of biomedical researchers, to the practicing physician and to the public in order to contribute promptly to the improvement of the Nation's health. The Institute's research is of profound importance to the public health since no subgroup of our population is immune to attack by the diseases which NIDDK addresses. Their collective economic burden exceeds \$100 billion annually. The more profound cost of these diseases in terms of human suffering cannot be measured.

## Research Focus—Diabetes, Endocrinology, and Metabolic Diseases

### Overview

The Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEMD) supports extramural research related to diabetes and its complications, to endocrinology and a variety of endocrine disorders, and to metabolism and metabolic diseases, including cystic fibrosis.

### Diabetes

The Diabetes Research Program supports research covering a wide range of fundamental and clinical



*NIDDK places a strong emphasis on basic research because the etiologies of many of the diseases involved are unknown. (above)*

*The portable insulin pump administers insulin in a continuous fashion and adjusts dosage for meals and exercise. (right)*

studies related to the etiology, pathogenesis, prevention, diagnosis, treatment, and cure of diabetes mellitus and its complications. Specific areas of research interest encompass the structure/function of the pancreatic hormones and related peptides and enzymes, including biosynthesis, secretion, and mechanisms of action; carbohydrate, lipid, and protein metabolism; and nutritional interrelationships including obesity. Other areas of research interest include studies of the genetic nature of diabetes and identification of specific markers which characterize individuals predisposed to diabetes; studies to assess immunologic, infectious and environmental factors as they relate to diabetes; and studies related to nutrition, metabolic regulation, and hormone synthesis/secretion/action with respect to the pathobiology of diabetes mellitus and its sequelae. In addition, the program also provides support for studies related to



*Retinopathy can lead to blindness for patients with diabetes. New research suggests that measuring a growth factor in the blood may identify patients at high risk for vision loss.*

pancreas and islet transplantation, automated insulin delivery systems and glucose sensors, the psychosocial and behavioral aspects of diabetes, and the epidemiology of diabetes and its complications.

#### *Endocrinology*

The Endocrinology Research Program supports basic and clinical studies of normal and abnormal function of the pituitary, thyroid, parathyroid, adrenal, pineal, and thymus glands. A substantial portion of the program is devoted to structure/function studies of the hypothalamic factors that regulate endocrine functions. Studies of the mode of action of hormones, their biosynthesis, secretion, metabolism, binding to protein carriers, and effects on target tissues, as well as characterization of hormone receptors represent a major component of the program. The program also supports studies of hormone-like agents produced by a number of tissues including somatomedins, growth factors and cytokines, gut and brain peptide hormones, vitamin D metabolites and prostaglandins.

#### *Metabolic Diseases*

This program supports research studies on (1) synthesis and biosynthesis of steroid and peptide hormones and related drugs; (2) membrane structure and function with special emphasis on transport phenomena, role of cations, and topology of the cell surface; (3) enzyme and other protein structure and function relevant to understanding of intermediary metabolic processes and their regulation. Methodologies supported span the domains of biophysics (instrumental techniques), biochemistry (purification and mechanistic aspects) and physiology (transport); (4) enzyme biosynthesis with special emphasis on genetic control of synthesis; (5) normal and abnormal carbohydrate, fat, amino acid, urea, pyrimidine and purine metabolism *in vitro* and *in vivo* (e.g., cell and tissue cultures, bacterial and animal models, humans, etc.); and (6) basic and clinical aspects of etiology, pathogenesis, prevention and treatment of inherited metabolic

disorders (aminoacidopathies, hyperuricemias, organic acidurias, urea cycle disorders, mucopolysaccharidoses, glycogen storage diseases, etc.).

#### *Cystic Fibrosis*

This program supports investigator-initiated research related to the metabolic aspects of cystic fibrosis (CF), nutritional aspects of CF, and a variety of other CF-related topics including the development of methods for homozygote and heterozygote screening. In addition, the program supports a cystic fibrosis research center as well as a mutant cell repository that serves as a resource for scientists studying various aspects of cystic fibrosis.

#### *Program Highlights*

These major programs support investigator-initiated research related to diabetes, endocrinology, and metabolic diseases. The Division also supports research training through both National Research Service Award fellowships and institutional training grants. Physician Scientist Awards, Clinical Investigator Awards, Research Career Development Awards, and senior fellowships provide additional options for highly qualified individuals to pursue further development of research careers in areas of

outstanding scientific opportunity.

The Division supports the following special programs:

#### *Research Centers*

There are two types of centers in the area of diabetes. Biomedical research and research training is the sole focus in each of the five Diabetes-Endocrinology Research Centers (DERCs); the seven Diabetes Research and Training Centers (DRTCs) also include training of medical and allied health professionals, continuing education, and model demonstration and outreach activities. A congressionally mandated report on activities and accomplishments of the DRTCs is being published separately.

#### *Clinical Trials*

Through the Cooperative Agreement and Contract mechanisms, the Division supports the Diabetes Control and Complications Trial (DCCT), a multicenter, randomized, controlled study to determine if maintenance of near-normal levels of blood glucose will prevent, delay, or ameliorate the early vascular complications of type I diabetes (IDDM). During 1985, the Division completed a 2-year study to assess the feasibility of conducting the full scale multicenter DCCT. Two independent advisory groups unanimously recommended that the



*The Diabetes Research and Training Centers also engage in training of medical and allied health professionals.*

Institute proceed with the DCCT, and recruitment was initiated subsequently for a total of 1400 patients for the full scale, long-term clinical trial. Several NIH Institutes contributed significant resources and technical assistance in support of the DCCT during this period, and various commercial organizations donated supplies, equipment, and services with a market value exceeding \$1 million.

#### *Research Resources*

Through contracts and interagency agreements, the DDEMD supports a number of specialized research resources that are not otherwise available to the scientific community. These resources currently include various pituitary hormones and reagents, steroid hormones, human tissues and organs, isolated human chromosomes, human mutant cell lines, a DNA sequence library, and a rat model of diabetes.

#### *Requests for Proposals*

Publication of Requests for Proposals (RFPs) represents a formal mechanism to solicit contract proposals from the extramural community to provide goods or services required by the Division for programmatic purposes. These include:

- Production and Distribution of BB/W Rats
- Collection of Human Pituitary Glands
- Extraction of Human Pituitary Hormones
- Extraction of Animal Pituitary Hormones
- Distribution of Hormones and Reagents
- Analysis for WHO Multinational Study
- Small Business Innovative Research Projects

#### *Interagency Agreements*

During this period, the following interagency projects were initiated:

- Infectivity Testing of Human Growth Hormone Preparations
- Epidemiologic Followup of Human Growth Hormone Recipients
- Development of a DNA Sequence library

- Production and Distribution of Isolated Human Chromosomes

- Production and Distribution of Mutant Cell Lines from Families of Patients with Cystic Fibrosis

#### *National Hormone and Pituitary Program (NHPP)*

On April 19, 1985, the Institute suspended general distribution of pituitary-derived human growth hormone (hGH) for use in clinical research following reports of three deaths from Creutzfeldt-Jakob disease in individuals who had previously received hGH through this program. In conjunction with the recommendations of a special Interagency Coordinating Committee convened by the Assistant Secretary for Health, the program staff assisted in the initiation of infectivity studies to test all batches of human growth hormone that had been previously administered and to develop an epidemiologic followup of patients who had previously received hormones through this program. The NHPP continues to distribute human and animal pituitary hormones and antisera for use in nonclinical endocrine research.

#### *National Diabetes Data Group*

This congressionally mandated program provides a national focus for the collection, analysis, and dissemination of data on diabetes and its complications. The DDEMD program staff is assisted by advisors with expertise in the clinical, epidemiologic, and socioeconomic aspects of diabetes and by representatives of various Federal agencies, professional societies, voluntary health organizations, and the National Diabetes Advisory Board. One major accomplishment of the data group during this period involved publication of *Diabetes In America*, a 680-page, 32-chapter assessment of data related to diabetes and complications in the United States. In addition, the data group developed new recommendations regarding the classification and diagnostic criteria for diabetes which were presented to a WHO study group. The data group also contributed to analyses to develop norms and standards for plasma

glucose levels and to determine the prevalence of undiagnosed diabetes and impaired glucose tolerance.

#### *National Diabetes Information Clearinghouse (NDIC)*

This program is also congressionally mandated, and provides a Federal focus for the collection and dissemination of information and educational materials, programs, and resources related to diabetes and its complications.

Staff members of both programs are assisted by advisors with expertise in the clinical, educational, and behavioral aspects of diabetes and by representatives of various Federal agencies, professional societies, voluntary health organizations, and the National Diabetes Advisory Board. During this period, the third edition of the *NDIC Compendium* was published. This provides a description of educational programs, materials, and selected pilot and feasibility studies sponsored by various Federal programs, professional societies, and voluntary health organizations. In addition, under leadership of the clearinghouse, the Combined Health Information Database was made available for public access through a major data base vendor.

#### *WHO Collaborating Center*

This center was recently established within the DDEMD to link expertise needs and resources in the United States related to diabetes research, information, and education with those of WHO member nations internationally.

#### *Endocrinology Program Advisory Committee*

In 1986, the Division established this expert committee to advise and assist the staff in identifying new and emerging needs and opportunities in areas of research related to endocrinology and endocrine disorders within the purview of NIDDK. It is anticipated that this committee will also serve in an advisory capacity with respect to the acquisition and distribution of research resources through the National Hormone and Pituitary Program.

### *Program Announcements*

Publication of a Program Announcement (PA) represents a formal mechanism for the Division to notify the scientific community regarding new, emerging, and established areas of general programmatic interest. Some examples of PAs published in 1985 include the following:

- Autoimmunity Related to Endocrine Diseases
- Effects of Environmental Agents on the Endocrine System
- Use of New Techniques to Study Metabolic Processes
- Endocrine Regulation of Bone Metabolism

### *Requests for Applications*

Publication of Requests for Applications (RFAs) represents a formal mechanism to solicit grant applications from the scientific community in specific areas of research which have been identified by the Division. Major initiatives announced in 1985 include:

- Clinical Centers for the Diabetes Control and Complications Trial
- Genetic and Metabolic Defects Underlying Cystic Fibrosis
- Shared Scientific Instrumentation Grants
- Small Grants for Research on Inherited Metabolic Diseases

### *Workshops and Conferences*

During this period, the DDEMD staff has organized workshops and conferences in the following areas:

- Pancreatic Islet Transplantation
- Mechanism of Action of Thyroid Hormone
- Mapping, Cloning, and Manipulating Genes
- Epithelial Cell Culture in Cystic Fibrosis
- Nutrition in Cystic Fibrosis
- Future Directions for the National Hormone and Pituitary Program
- Diagnostic Criteria for Diabetes
- Career Opportunities in Diabetes Research

### *Program Development Activities*

During FY 1985-86, the DDEMD staff consulted widely with leaders in the scientific community in developing and implementing program plans and in establishing and refining priorities for long-term program objectives.

During the coming year, the DDEMD will continue to accord the highest priority to investigator-initiated research projects. The Division is also considering development of new programmatic initiatives in the following areas:

#### *Interdisciplinary Research in Diabetes and Endocrinology*

Plans are being developed to expand support of core centers and to initiate specialized centers of research in areas of high priority to the Division's research programs.

#### *Facilitation of Research in Endocrine Transplantation*

This initiative includes specialized research resources, a pancreas/islet cell transplant registry, multicenter collaborative research programs, transplant research training programs, and periodic transplant research conferences.

#### *Use of Human Tissues in Biomedical Research*

This initiative proposes a major expansion of current efforts to promote the acquisition and distribution of human tissues for research purposes.

#### *Establishment of a National Diabetes Data System*

Plans are being developed by the DDEMD to provide for the system as recently authorized by Congress.

#### *Cost Recovery for Research Resource Programs*

Plans are being developed by DDEMD staff to institute user fees to offset the costs of maintaining various specialized research resources.

#### *Survey of Physician Practice Behaviors*

This initiative proposes to survey the current attitudes and practices of physicians with respect to the treatment of people with diabetes.

*Treatment of Diabetic Nephropathy*  
A multicenter clinical trial is proposed to study the impact of intervention in the prevention of end-stage renal disease in patients with diabetes.

#### *Treatment of Short Stature*

A multicenter clinical trial is proposed to assess new therapeutic opportunities in the treatment of short stature in children.

#### *Consensus Development Conference*

Plans are being finalized for this conference, which will focus on diet and exercise in the clinical management of noninsulin-dependent diabetes.

#### *Research Conferences*

Plans are being developed for the following workshops and conferences:

- Self Monitoring of Blood Glucose
- Stimulus-Secretion Coupling in Pancreatic Islet Cells
- Impaired Glucose Tolerance
- Noninvasive and Implantable Glucose Sensors
- Noninvasive Techniques to Study Metabolic Processes
- Three-Dimensional Structure of Hormones and Receptors

### *Highlights of Research Advances*

The following section briefly highlights a few of the areas in which the Division of Diabetes, Endocrinology, and Metabolic Diseases has reported recent progress in its research programs.

#### *Diabetes*

• *Etiology of insulin-dependent diabetes.* Insulin is the product of the beta cells that are a component of the islets of Langerhans in the pancreas. At diagnosis, patients with insulin-dependent diabetes (IDDM or type I diabetes) are found to have antibodies directed against their own islet cells, a suggestion that IDDM is an autoimmune disease. Examination of blood samples (sera) of relatives of patients with IDDM who were, like IDDM patients, positive for islet cell antibodies showed that about 32

percent of these relatives also had insulin autoantibodies. Since these serum samples had often been collected years before, current data could be compared. Several relatives who were positive for these antibodies had developed clinical IDDM. The data indicated that the presence of insulin antibodies is a marker for the subsequent development of IDDM, and that the simultaneous presence of islet cell antibodies and insulin autoantibodies was associated with a greater risk of developing IDDM than the presence of either marker alone. Measurement of insulin autoantibodies is easy to perform on a large scale and is likely to be specific for autoimmunity directed against the insulin-secreting beta cell; consequently, it should be very useful in screening for and identifying individuals likely to develop diabetes.

- *The insulin receptor gene.* Two groups of NIDDK-supported researchers have reported the complete structure of the human insulin receptor, based on the DNA sequence of the genes coding for the insulin receptor, from human placenta.

In less than 1 year from the cloning of the gene, the same two teams of investigators have published exciting experiments that would not have been possible before and which are allowing us to unravel the mystery of how insulin works. One team has located the site on the insulin receptor responsible for transmitting the hormone's message to the interior of the target cell. This may contribute to the definitive elucidation of the physiologic role for this primary aspect of insulin action. The other has introduced the cloned human receptor gene into the cells of a different species. This cloning trick resulted in the expression of functional, insulin responsive receptors in a simplified environment that allows them to dissect the function of the insulin receptor.

- *Regulation of insulin biosynthesis by glucose.* A novel feature of insulin synthesis in the islets of Langerhans is that the synthesis is

strongly controlled by glucose. Recent studies have examined how glucose exerts this control. Sophisticated techniques are required to study the rate of synthesis and synthetic mechanisms. Glucose has been found to stimulate the rate at which the precursor of insulin (preproinsulin) is synthesized, by stimulating several of the complex steps. Glucose also decreases the rate at which the template for the synthesis of preproinsulin (insulin messenger RNA) is degraded. These findings provide new insights into normal islet cell mechanisms regulating insulin production that may be deranged in various forms of diabetes.

- *Epidemiologic evidence on cardiovascular and eye disease risks in diabetes.* At least half of the excess coronary heart disease in diabetic women has recently been shown to be due to diabetes per se and not to other cardiovascular risk factors. In a study of 120,000 nurses during 1976-80, diabetic women had a fourfold higher risk of nonfatal myocardial infarction and a sevenfold higher risk of fatal coronary heart disease. After statistical adjustment for the classic risk factors of hypertension, cholesterol, smoking, obesity, and family history the risks remained excessively elevated, at threefold above those for nondiabetic women. These findings support the need for medical strategies beyond routine management of coronary risk factors in women with diabetes.

Severe eye disease is a devastating complication of diabetes, but recent research indicates that genetic factors do not play a role in its development in patients with insulin-dependent diabetes (IDDM). Among 116 families with two or more diabetic offspring, in a cohort of 1966 IDDM cases, there was no evidence of familial association for severe diabetic eye disease after the effect of diabetes duration was taken into account. This finding suggests that alteration of environmental and lifestyle factors should be targeted in an effort to reduce this microvascular complica-

tion of diabetes. In contrast, there was familial association for cardiovascular disease, suggesting that this complication of diabetes may be connected with inheritance.

### *Endocrinology*

- *Cellular response to hormones in aging.* Specific serum factors are involved in the control of cell division, including peptides with growth-promoting, insulin-like properties, called somatomedins. One of these, somatomedin C (SM-C), stimulates cell division in cultured human fibroblasts and is thought to be the mediator by which growth hormone affects cell growth.

When fibroblasts from young donors were preincubated with glucocorticoid (adrenal steroid hormone), there was a marked increase in the response to SM-C. Glucocorticoid enhanced SM-C stimulation of both DNA synthesis and cell multiplication. In contrast, in cells from aged donors or from a child with a disease causing severe accelerated aging (progeria), glucocorticoid did not enhance the effect of SM-C. Glucocorticoid itself has no effect on fibroblast multiplication. The diminution with aging of the capability of cells to divide or regenerate may be due in part to an impairment in the synergism between SM-C and glucocorticoids observed in cells from young donors.

- *Communication between the immune and neuroendocrine systems.* Glucocorticoid levels increase during stresses such as infection, and this has been attributed to alterations in the hypothalamic and pituitary hormones, corticotropin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH), which regulate adrenal production of glucocorticoids through a hypothalamic-pituitary-adrenal axis. It is now becoming evident that in addition to neuroendocrine system control of immune function, there is bidirectional communication between the neuroendocrine and immune systems, such that the immune system itself regulates endocrine responses.



New data suggest that the gene that encodes ACTH in the pituitary gland can be expressed and similarly controlled in leukocytes. Further, virus infection or bacterial endotoxin treatment increases ACTH production by lymphocytes.

In addition, it is clear that monocyte-derived factors (monokines) activate the pituitary-adrenal axis and increase glucocorticoid levels, which may then directly affect the immune and inflammatory response, including inhibition of further production of monokines.

#### *Metabolic Diseases*

- **Fabry's Disease:** enzyme replacement is feasible due to cloning of the gene. Fabry's disease is a rare genetic disorder that results from the inherited deficiency of the enzyme alpha-galactosidase A. This leads to the accumulation of a particular complex fat in the blood plasma and in cells lining the blood vessels, narrowing the blood vessels and depriving downstream tissues of oxygen and nutrients.

Investigators have now succeeded in overcoming a major difficulty in cloning this enzyme's gene, the problem of low enzyme concentration in cells. Human gene libraries were constructed in viruses that could infect bacteria. The infected bacteria produced a very small amount of alpha-galactosidase A, which was detected with an antibody to the enzyme. Short DNA sequences corresponding to parts of the enzyme protein were chemically synthesized and used as probes to confirm that the gene isolated by the antibody method was indeed that for alpha-galactosidase A.

This advance has opened up the opportunity for the treatment of Fabry's disease by alpha-galactosidase A replacement using bacteria as a factory for production of the human enzyme. The potential now exists to produce unlimited quantities of this enzyme for eventual therapeutic purposes.

- **Defective gene in cystic fibrosis localized to chromosome 7.** Cystic fibrosis (CF), the most common lethal inherited disease in Caucasians, has long been known to be the result of a defective gene.

As a first step in the isolation of the defective gene responsible for cystic fibrosis, scientists have sought rough genetic markers to localize the gene to a specific chromosome. In late summer of 1985, researchers reported finding such a marker that located the cystic fibrosis gene on chromosome 7. In November, several groups working independently found two new genetic markers that appear to be even closer to the target gene. The overlap between the various markers locates the cystic fibrosis gene in the middle of the long arm of chromosome 7. On the basis of genetic analysis, investigators examined DNA samples from families with children with cystic fibrosis and discovered they could predict which children were afflicted with the disease.

Although the new marker for the cystic fibrosis gene allows detection of the gene in DNA samples from members of families where there is a known case of cystic fibrosis, it is not specific enough to diagnose asymptomatic carriers in the general population. To detect asymptomatic carriers will require isolation of the cystic fibrosis gene itself.

### **Research Focus—Digestive Diseases and Nutrition**

#### **Overview**

The Division of Digestive Diseases and Nutrition (DDDN) has responsibility for managing research programs related to liver and biliary diseases, pancreatic diseases, gastrointestinal diseases, including neuroendocrinology, motility, immunology, and digestion in the GI tract, nutrient metabolism, obesity, eating disorders, and energy regulation.

The different categories of award mechanisms utilized in this process have been described above. In addition, the Division provides leadership in coordinating activities related to digestive diseases and nutrition throughout the National Institutes of Health and with various other Federal agencies. The reader's attention is directed to a



*Patients with duodenal ulcers confirmed by endoscopy participated in a recent clinical trial. The study compared the effectiveness of two different drugs in healing ulcers and preventing their recurrence.*

detailed, congressionally mandated report on the Division's program of digestive diseases and nutrition centers which is being published separately.

#### **Digestive Diseases Branch**

The Liver and Biliary Program supports basic and clinical research into the normal function and the diseases of the liver and biliary tract. Areas of basic research include studies on: factors initiating and maintaining hepatic regeneration; factors leading to liver cell injury, fibrosis, and death; basic and applied studies on liver transplantation, including techniques of preservation and storage; metabolism of bile acids and bilirubin; physiology of bile formation; factors controlling cholesterol levels in bile; and gallbladder and bile duct function. Areas of disease research include: cholesterol and pigment gallstones; inborn errors in bile acid metabolism; chronic hepatitis that evolves from autoimmune, viral, or alcoholic disease; and various liver diseases.

The Pancreas Program encourages research into the structure, function, and diseases (excluding cancer and cystic fibrosis) of the exocrine pancreas. Areas of research interest include: hormonal and neural regulation of electrolyte, fluid, and enzyme secretion; receptors for secretagogues (agents that stimulate secretion); stimulus-secretion cou-



pling mechanisms; gut-islet-acinar interrelations; organization and expression of pancreatic genes; protein synthesis and export; tissue injury, repair, and regeneration; physiology and pathology of trophic responses; innervation; transcapillary solute and fluid exchange; pancreatic transplantation, storage, and preservation and acute and chronic pancreatitis (and relevant experimental models).

The Gastrointestinal Neuroendocrinology Program supports both basic and clinical studies on normal and abnormal function of the enteric nervous system and the central nervous system elements that control the enteric nervous system. Neuroendocrine studies supported include: histochemistry and neurochemistry, electrical properties of enteric ganglion cells, chemical neurotransmission, neural control of effector function, and extrinsic nervous input. This program places a great deal of emphasis on gastrointestinal hormones and peptides. In addition, the program also supports studies on disease conditions associated with excessive or

deficient secretions of neuropeptides.

The Gastrointestinal Digestion Program supports research on the process of food digestion in the gastrointestinal tract (GIT) including the synthesis and assembly of digestive enzymes; the transport of water, ions, sugars, amino acids, peptides, lipids, vitamins, and macromolecules. Other areas of research focus on the regulation of gene expression in the developing GIT; the structure and function of the gut mucosa; the growth and differentiation of gastrointestinal cells in normal and disease states; intestinal transplantation, storage, and preservation; and gastrointestinal tissue injury, repair, and regeneration. Also supported are studies on gastrointestinal diseases such as maldigestion and malabsorption syndromes.

Investigators supported by the Gastrointestinal Motility Program focus their research on the structure of gastrointestinal muscles, the biochemistry of contractile processes and mechanochemical energy conversion relations between

metabolism and contractility in smooth muscle, extrinsic control of digestive tract motility, and the fluid mechanics of gastrointestinal flow. Other studies and areas of interest include the actions of drugs on gastrointestinal motility, intestinal obstruction, and diseases such as irritable bowel syndrome (functional digestive disorders), colonic diverticular disease, swallowing disorders, and gastroesophageal reflux.

The research emphasis of the Gastrointestinal Immunology Program focuses on intestinal immunity and inflammation. Areas of interest include: ontogeny and differentiation of gut-associated lymphoid tissue; migratory pathways of intestinal lymphoid cells; humoral antibody responses; the role of cytotoxic (cell-killing) effector cells in chronic intestinal inflammation; genetic control of the immune response at mucosal surfaces; immune response to enteric antigens in both intestinal and extraintestinal sites; granulomatous inflammation; lymphokines (factors released by sensitized lymphocytes) and cellular immune regulation; leukotrienes/prostaglandin effects on intestinal immune responses; T-cell mediated intestinal tissue injury; the intestinal mast cell and its role in intestinal inflammation; approaches to optimal mucosal immunoprophylaxis, including viral, bacterial, and parasitic diseases; and diseases such as gluten sensitive enteropathy, inflammatory bowel disease, and gastritis.

#### **Nutritional Sciences Branch**

The Nutrient Metabolism Program supports basic and clinical studies related to the requirement, bioavailability, and metabolism of nutrients and other dietary components at the organ, cellular, and subcellular levels in normal and diseased states. Specific areas of research interest include the understanding of the physiological function and mechanism of action/interaction of nutrients within the body; the effects of environment, heredity, stress, drug use, toxicants,



*New noninvasive diagnostic tools provide safer, more effective ways of identifying disorders of the digestive system.*



*Good nutrition comes in a multitude of forms.*

and physical activity on problems of nutrient imbalance and nutrient requirements in health and disease; specific metabolic considerations relating to alternative forms of nutrient delivery and use, such as total parenteral nutrition, and improved methods of assessing nutritional status in health and disease.

The Obesity, Eating Disorders, and Energy Regulation Program emphasizes research on the biomedical and behavioral aspects of obesity, anorexia nervosa, bulimia, and other eating disorders. The goals of such research are to establish a clear understanding of the etiology, prevention, and treatment of these multifaceted conditions. Areas of research interest focus on the physiological, metabolic, psychological, and genetic factors that affect food choices, food intake, eating behavior, appetite, and satiety; the effects of taste, smell, and gastric and humoral (including neurotransmitter) responses in association with dietary intake and subsequent behavior; the physiological and metabolic consequences of weight loss or weight gain; the effect of mild exercise on appetite and weight control, and the individual variability in energy utilization and thermogenesis.

### **Special Programs Branch**

#### *Research Training and Career Development Program*

This program offers research training and career development awards in support of the programs of the Division of Digestive Diseases and Nutrition. Three types of National Research Service Awards and three types of research career development awards are available.

#### *Research Centers Program*

The Digestive Diseases Centers Program provides center grant support for integrating, coordinating, and fostering interdisciplinary cooperation between groups of established investigators who conduct programs of high-quality research that relate to a common theme in digestive disease research. The current centers include research foci on liver diseases, gastrointestinal motility, absorption and secretion processes, inflammatory bowel disease, structure/function relationships in the gastrointestinal tract, neuropeptides and gut hormones, and diarrheal diseases.

The Clinical Nutrition Research Units (CNRU) Program supports centers of excellence, each of which integrates research, educational, and service activities focused on human nutrition in health and disease. The CNRU serves as the focal point for

an interdisciplinary approach to clinical nutrition research and for the stimulation of further research. The Division is currently funding five CNRUs. Through the CNRU mechanism, the NIH has made great strides toward upgrading the role of clinical nutrition in the participating institutions.

Both the CNRUs and the Digestive Disease Centers are supported by the core center grant mechanism. The core center grant provides funds for (1) core resources such as cell culture, immunoassay, biostatistics, or other central research service facilities; (2) pilot/feasibility projects, which support new investigators or investigators from other fields who wish to pursue new and innovative ideas to a point where they can compete for independent support; (3) program enrichment funds to provide for small conferences or symposia, and special consultants for the center; and (4) in the case of the CNRUs only, a position for a new investigator.



*Clinical Nutrition Research Unit awards stimulate progress in nutrition research, patient care, and nutrition information for the public.*

*U.S.-Japan Malnutrition Panel*  
In 1965, President Lyndon B. Johnson and Japanese Prime Minister Eisaku Sato issued a joint communique recognizing their mutual concern for the health and well-being of all the peoples of Asia. This effort led to the foundation of the U.S.-Japan Cooperative Medical Science program, which operates within a bilateral government framework. The Malnutrition Panel was established in 1966 to foster and support investigator-initiated research to help alleviate the serious problem of malnutrition.

*National Digestive Diseases Information Clearinghouse*  
The National Digestive Diseases Information Clearinghouse (NDDIC) functions as the central point for the collection and dissemination of information and education materials concerning programs and resources relevant to digestive diseases. The Clearinghouse works closely with local and national digestive disease organizations, professional groups, and Federal and state agencies. The overall goals of the NDDIC are to increase knowledge and understanding about digestive diseases among patients, health professionals, and the public and to function as a catalyst in assisting and enhancing the efforts of these various groups in the development and exchange of educational materials and digestive diseases information.

*Epidemiology and Digestive Diseases*  
The Epidemiology and Digestive Diseases Data Base System serves as the major Federal focus for the collection, analysis, and dissemination of data on digestive diseases and their complications. Drawing upon the expertise of the research, medical, and lay communities, the Data Base System initiates efforts to: (1) define the data needed to address the scientific and public health issues in digestive diseases; (2) foster and coordinate the collection of these data from multiple sources; (3) promote the timely availability of reliable data to pertinent scientific, medical, and public

organizations; (4) modify data-reporting systems to identify and categorize more appropriately the medical and socioeconomic impact of digestive diseases; and (5) promote the standardization of data collection and terminology in clinical epidemiological research.

### **Program Highlights**

The major accomplishment of the DDDN program was the reorganization of the Divisional research program to that presented above. Over the last 10 years the program has experienced rapid growth, and at this point a complete review and program reorganization were essential. In addition, these accomplishments may be mentioned:

#### *Prospects for Effective Nonantimicrobial Antidiarrheal Agents*

Participants in this conference reviewed the need, state of scientific knowledge, and prospects for effective antidiarrheal agents to develop a planning document to guide the Division in this area of investigation.

#### *U.S.-Japan Malnutrition Program*

This conference focused primarily on providing solutions to problems that affect the undernourished of Asia. The most common states of undernutrition are protein energy malnutrition and iron and vitamin A deficiencies. A malnutrition symposium addressed these concerns. The program also sponsored a workshop on calcium metabolism and aging, and a workshop to revitalize the research priority areas of the malnutrition panel.

#### *Anorectal Disorders, a Workshop on Clinical Trials*

Anorectal diseases and disorders represent a major national problem in terms of morbidity. Diseases and disorders considered in this meeting included hemorrhoids, fissures, fistulas, proctitis, rectal prolapse, constipation, and fecal incontinence. Participants in this meeting recommended consideration of a clinical trial on anorectal Crohn's disease (chronic inflammation of the gastrointestinal tract), and an initia-

tive to standardize terminology used for hemorrhoids, as important steps in the development of this field.

#### *Ad Hoc Conference on Liver Heterotransplantation*

This conference was held at the Kennedy Institute for Ethics. The issue of liver heterotransplantation was considered by bioethicists and researchers, to provide new insight to investigators and their institutions on the complex ethical issues associated with liver transplantation.

### **Program Development Activities**

Initiatives planned or proposed include the following:

- Assessment of Accomplishments of Digestive Diseases and Nutrition Centers Program
- Training of Digestive Diseases Epidemiologists
- The Nerve-Gut Axis and Functional Bowel Disease: Encouragement of Research
- Research on Oral and Parenteral Lipid Nutritional Requirements and Sources
- The Role of Mucus in the Protection of the Gastrointestinal Mucosa: Research is Needed
- Conference on Mechanisms of Liver Cell Death
- Biological Mechanisms of Omega-3 Fatty Acids in Health and Disease States
- Liver Tissue Procurement and Distribution System for Discarded Tissue from Liver Transplant Recipients
- Exocrine-Endocrine Pancreas Interaction
- Research on Mechanisms of Fecal Continence and Anal Function

### **Highlights of Research Advances**

The following section briefly highlights some of the areas in which the Division of Digestive Diseases and Nutrition has reported recent progress in its research programs.

#### *Digestive Diseases*

- *Liver transplantation.* Up until the early 1980's, only one center in the United States was performing

liver transplants, and 1-year survival rates were about 30 percent. However, with improvements in surgical techniques, careful selection of patients, and the introduction of the powerful drug cyclosporin to prevent rejection, the results of liver transplantation have markedly improved. Today 70 percent or more of liver transplant patients live for at least 1 year.

- **Peptic ulcers.** NIDDK-supported research contributed to the development in the 1970's of new drugs such as cimetidine, ranitidine, and sucralfate, which have dramatically improved the outlook for people with peptic ulcers. Today, one of the most promising areas of ulcer research is the study of brain-gut peptides and their role in controlling gastric acid secretion.

- **Gallstones.** A major advance in NIDDK-funded gallstone research has been an improved understanding of the processes that cause gallstones to form in cholesterol-saturated bile. Results of this research not only have led to the development of agents that can dissolve cholesterol gallstones, but also may lead to the development of ways to prevent gallstone formation.

- **New treatment removes gallstones without major surgery.** NIDDK grantees have successfully dissolved cholesterol gallstones in 18 patients using methyl tert-butyl ether (MTBE), a liquid used as a common laboratory solvent and as an octane enhancer in gasoline. The technique, performed under local anesthesia, involves the placement of a catheter (a thin, flexible tube) through the abdomen into the gallbladder. Small amounts of MTBE are then injected through the catheter and continuously flushed into and out of the gallbladder. The scientists report that in seven patients, stones completely dissolved within 12 hours and that most of the stones in the remaining patients dissolved within 25 hours. In addition, side effects are minimal because any residual MTBE is rapidly absorbed from the gut and exhaled through the lungs.

Persons undergoing MTBE treatment usually require an average hospital stay of 4 days and can return to work a few days later, whereas a standard gallstone operation usually requires at least a week in the hospital and 6 to 8 more weeks of recovery, if there are no complications.

### *Nutrition*

- **Obesity: Abnormal physiology and fat distribution.** Obesity and its associated diseases constitute some of the more serious health issues of the Nation, and yet they remain refractory to research efforts to understand their pathogenesis and to develop treatments based on such understanding.

Mechanisms by which the anatomic distribution of adipose (fat) tissue is controlled in man are important since it is now recognized that abdominally situated adipose tissue is a greater risk factor for obesity-associated disorders such as type II diabetes mellitus, hypertension, and hypertriglyceridemia than equivalent degrees of adiposity in the gluteal (buttocks) or other regions. Understanding of the cellular interaction and control of metabolism in these systems could have profound consequences for the goals and methods of prevention and treatment in obesity.

Breakdown of lipids (lipolysis, associated with beta-adrenergic responsiveness) is greater in abdominal subcutaneous than in gluteal subcutaneous fat tissue in both sexes. However, the greater alpha-2 (antilipolysis) adrenergic responsiveness of the female gluteal site may explain the tendency to greater accumulation of gluteal adipose tissue in females as compared to males.

### **Research Focus—Kidney, Urologic, and Hematologic Diseases**

#### **Overview**

The Division of Kidney, Urologic, and Hematologic Diseases conducts a variety of activities to support and stimulate research within its subject areas, assists in identifying new research opportunities, assesses

research progress, and publicizes findings and new methods of treatment. The Division staff meets with scientists who share new knowledge and advise the Institute on advances; opportunities, and high-priority research needs. The Division publishes program announcements and requests for research grant applications or Proposals in the areas of high-priority research needs. The Division also publishes scientific and educational materials and information concerning new research directions. The different categories of award mechanism utilized by the Division in pursuit of its mission have been described above.



*New techniques are improving the ability of artificial kidneys to remove poisonous wastes from the blood.*

The programs of this Division are keyed to important public health problems. They address, among other subject areas, the underlying mechanisms of kidney disease through studies of normal structure and function of the kidney, including its metabolism, transport, and fluid-electrolyte dynamics; the metabolic and systemic abnormalities of chronic renal disease and end-stage renal failure; and urinary tract infection, neuromuscular disorders of bladder function,

obstruction, and urolithiasis (kidney stone disease). The Division's Hematology Program supports investigations into basic mechanisms of normal blood cell function and into pathogenesis of hematologic disorders, including development of treatment and prevention modalities, clinical application, and evaluation of treatment.

### **Program Highlights**

Activities of the Division undertaken during this time period included the following:

#### *Benign Prostatic Hyperplasia:*

##### *A Symposium*

A second conference on benign prostatic hyperplasia (BPH) was held on May 16-19, 1985. The symposium brought together a multidisciplinary group of investigators including 130 invitees from Europe and the United States. The proceedings will be published in late 1986. As a result of the meeting, a new program announcement was issued (see below).

#### *Conference on Cell/Tissue Culture Techniques in Renal Research*

A conference was held to bring together investigators in the mainstream of developing and using cell/tissue culture techniques. Some 225 scientists attended, representing academic institutions, government, industry, and a multitude of scientific disciplines. The 2-day conference covered the areas of cell biology, growth and growth factors, inflammation, and molecular genetics. It is anticipated that this meeting will expand the scope of current studies in this field by introducing research relating to cell biology and genetics.

#### *Diet and Kidney Disease: Early Progress on a Clinical Trial*

The charge to the Institute is to plan, conduct, and report the results of a single clinical study seeking to define the effect of dietary modifications (restriction of dietary protein and phosphate intake, etc.) on the course of progressive renal disease/renal insufficiency. Awards have been issued to six clinical centers, and to a data coordinating center that also houses the nutrition coordinating center.

Phase I resulted in the development of a research protocol, and a detailed manual of operations is completed. During Phase II, the feasibility of conducting the study using the established protocols will be tested. After appropriate adjustments to the protocol, the actual study will commence in July 1987. An interagency agreement with the Health Care Financing Administration (HCFA) has been completed for sharing the clinical costs of the study.

#### *Polycystic Kidney Disease*

Adult polycystic kidney disease (PKD) costs Medicare approximately \$180 million each year. The human costs and loss of productivity escalate this figure even further. Very little is known about the natural history and pathogenesis of this disease. Two academic centers in the United States and another in Denmark have been identified and have begun to study large PKD patient populations. The NIDDK is providing funds for interdisciplinary studies in PKD patients.

#### *International Conference on Kidney Toxicity Caused by Drugs*

The NIADDK cofunded the International Conference on Drug-Induced Nephrotoxicity, on September 24-27, 1985, in Antwerp, Belgium. The conference was devoted to the major classes of drugs responsible for nephrotoxicity, including aminoglycoside antibiotics, cyclosporine, nonsteroidal anti-inflammatory drugs, lithium, and a miscellaneous group that includes antipyretic analgesics (fever- and pain-reducing agents) and minor anticancer drugs. The proceedings of the conference have been published in the *American Journal of Kidney Diseases*.

#### *International Workshop on Renal Insufficiency in Children*

The NIADDK cosponsored the Third International Workshop on Renal Insufficiency in Children, in Airlie, Virginia, on May 3-6, 1985. Chronic renal failure in children and the associated growth failure and hormonal/metabolic abnormalities were discussed. The proceedings of the conference were published in the *American Journal of Kidney Diseases*.

#### *Publication on Cooley's Anemia Therapy*

The Institute had primary responsibility for organizing a symposium (held in June 1984) entitled "New Research Approaches to Cooley's Anemia Therapy." The symposium summary was published in the *Annals of the New York Academy of Sciences* and will be distributed to grantees and other investigators and lay groups.

#### *Federal Interagency Coordinating Committee for Urological Research*

A Urology Coordinating Committee was appointed in response to a directive from the House Appropriations Committee. Members include the NIH, the Department of Defense, the National Science Foundation, and the Veterans Administration, as well as ad hoc members from the American Urological Association and the American Association of Clinical Urologists. A report that was submitted prior to the FY 1986 appropriations hearings was subsequently discussed at several meetings attended by urologists.

#### *Public Communication Efforts*

To increase public knowledge concerning diseases of the urinary tract, four radio broadcasts and one television appearance were scheduled on the topics of benign prostatic hyperplasia and urolithiasis. In addition, an exhibit on the causes of kidney stones was developed for display at HealthCare Expo '85 in Washington, D.C.

#### **Program Development Activities**

Working closely with its advisory groups and the scientific community, the Division is pursuing the following initiatives for development of future program efforts:

#### *Proposed Kidney and Urological Diseases Research Centers*

The establishment of a centers program was recommended to the Congress by the renal and urological communities, through the Intersociety Council on Kidney and Urological Diseases. These centers would investigate the causes of end-stage renal disease (ESRD) and would conduct research on immunologic mediated diseases,





*An appropriate proportion of research in future centers will be directed to clinical studies.*

diabetes mellitus and other endocrine and metabolic disorders, nephrotoxins and toxic cell injury, genetic abnormalities, developmental and obstructive disorders, and primary renal hypertension. The Division of Kidney, Urologic, and Hematologic Diseases supports the concept of kidney and urologic centers.

#### *Diabetes Mellitus Nephropathy in the Pima Indian Population*

- *Problem and Program.* This population, because of its unusually high prevalence of type II diabetes, provides a unique opportunity to study the onset, progression, and pathogenesis of diabetic nephropathy. In addition, this is a unique opportunity to establish and assess therapeutic intervention strategies. A request for contract proposals has been published and a final selection is expected to be made by August 1986. A central aspect of this contract will be the establishment of a

working group or task force of investigators, including several in the intramural program of NIDDK.

#### *Disease Mechanisms in Immunologic Renal Disease: A Program Announcement*

This announcement is intended to stimulate research on the role of the immune system in renal injury and to expand interdisciplinary research efforts by recruiting new scientists to enter the field. Although research in renal physiology has made significant advances, the techniques of basic immunology, genetics, and molecular biology have not been adequately applied to the kidney. In addition, research into the causes of the acceptance or rejection of renal transplants has been relatively neglected in modern clinical immunology.

#### *Request for Applications*

- *Molecular mechanism in renal transplantation.* Seven thousand end-stage renal disease patients undergo kidney transplants each year. There is need for closer

cooperation between basic immunologists and transplant physicians to exploit the advances in our knowledge about basic immunology in the care of kidney transplant recipients. This request for applications is intended to facilitate research on the molecular interactions between renal transplants and the immune system of the recipient, to develop new and more sensitive methods to measure renal transplant rejection, and to develop new modalities of immunosuppression by manipulating the molecules that cells use to communicate and proliferate.

- *A program to improve renal transplantation in children.* The purpose of this effort is to improve the basis for developing and selecting overall treatment strategies in children with ESRD, to delineate approaches to improve the outcome of renal transplantation in children, to evaluate side effects of therapy and their modulation in pediatric transplant recipients, and to identify and prioritize research needs in the areas of renal transplantation in children.

- *Epidemiology of end-stage renal disease.* The establishment of a National End-Stage Renal Disease Patients Registry is the focus of a Request for Proposals. The overall goals are to characterize the ESRD population; to establish prevalence and incidence rates of kidney diseases of differing etiologies (genetic, immune-related, environmental, toxic, infectious, etc.) that lead to ESRD; to document current maintenance dialysis therapies and match therapeutic regimens with specific patient outcomes; to provide data on which to base the rational prescription of different dialytic interventions; and to identify problems and opportunities for future investigation.

- *Isolation and characterization of the androgen receptor from prostatic tissue.* A Request for Proposals was issued to encourage research on the etiology and pathogenesis of benign prostatic hyperplasia.



• *Controlled clinical trial of hematin: therapy for acute porphyria attack.* A request for proposals is expected to stimulate the necessary collaborative efforts among experienced investigators. This clinical trial should provide objective and controlled data about the efficacy and safety of hematin therapy for acute porphyric attack, determine the optimal timing and dosage for hematin administration, and assess reported side effects.

• *Improved availability of blood cell precursors and growth factors: request for proposals.* Specific objectives of the contract activities anticipated are to develop techniques for obtaining homogeneous cell populations from hemopoietic culture systems for use by investigators, and to purify tenfold and make available hematopoietic factors currently in very short supply.

### Highlights of Research Advances

The following section briefly highlights a few of the areas in which the Division of Kidney, Urologic and Hematologic Diseases has reported recent progress in its research programs.

#### Kidney Diseases

• *Understanding the progressive nature of chronic renal disease.* Progression of renal disease following the initial insult to the kidney has been largely attributed to continued "activity" of the underlying disease that results in progressive loss of nephron (the filtration unit of the kidney) populations. A new postulate has been proposed, for which there is support from experimental data, that renal damage may progress even if the initial disease process has been eliminated. This "autoprogression" appears to commence when the initial damage reduces renal function to about 20 percent of normal. The cause of the damage appears to be increased blood pressure within the vasculature of the kidney, since the injury can be completely prevented by decreasing pressure even though flow remains high.

In a related finding, it has been shown in experimental animals with diabetes mellitus that increased

glomerular pressure (in the nephron) can lead to glomerular scarring even when renal mass has not been reduced.

Ongoing and planned experimental studies involving both nutritional and pharmacologic measures may ultimately lead to preventing the progressive loss of renal function in patients whose kidneys are at risk.

• *Accurate assessment of residual renal function.* The application of accurate techniques is critical in assessing glomerular filtration rates (GFR) to measure the rate of progression of renal insufficiency or in monitoring the effect of therapeutic interventions (dietary modifications in chronic renal disease, or immunosuppressive regimens in treating immune glomerular inflammatory diseases). This is important to physicians in monitoring drug therapy and to individuals who set public policy.

The standard means for measuring GFR is the renal clearance of a nitrogen-containing compound called creatinine. However, there is strong evidence now available indicating that creatinine as a marker to evaluate or monitor patients with chronic glomerular renal disease results in both gross and unpredictable overestimates of the GFR. Use of the substance inulin (an indigestible sugar found in plants), while preferable, has other disadvantages. Ideally, GFR should be measured by determining the clearance of a substance like inulin, one that is freely filtered through the glomerular capillary wall, is biologically inert, and is neither secreted nor reabsorbed by the tubules.

A major advance in estimating GFR has been the use of radio labeled (tagged with a radioactive isotope for tracing purposes) compounds that are excreted like inulin. A number of these, including sodium iothalamate, ethylene diaminetetra-acetic acid (EDTA), and diethylene triaminopenta-acetic acid (DTPA), have been shown to behave as true filtration markers in urine and plasma, providing the most accurate, rapid, and convenient way to determine the GFR in both the research and the clinical setting. Serial measurements of the plasma

clearance of these radioisotopes appear to be the most simple and accurate estimate of GFR values in patients with chronic renal insufficiency.

• *Linkage analysis of polycystic kidney disease.* In adult polycystic kidney disease (PKD), the most common heritable renal disease, each offspring of an affected parent has a 50 percent chance of inheriting the gene. Cyst development in the kidney is not retarded by any known therapy and leads to irreversible renal failure at a mean age of 51. Until recently, presymptomatic diagnosis depended on ultrasonographic detection of cysts, but exclusion of the diagnosis cannot be achieved by this means.

A 1985 study reported that in nine family pedigrees, the adult polycystic kidney disease locus was closely linked to a specific site (the  $\alpha$ -globin locus) on the short arm of chromosome 16. Linkage analysis was facilitated by the presence of a genetic marker (a "hypervariable region") associated with the globin locus. This is a small portion of DNA that is repeated back-to-back hundreds of times on chromosome 16. In practice this means that analysis of a family with classic PKD will identify a hypervariable marker of a particular size that is associated with the disease. If a fetus or child from that family carries this particular hypervariable marker, there is a great chance he or she will eventually prove to have PKD. These studies were carried out on families manifesting the most common phenotype of PKD. Further studies are needed, particularly in families with unusual clinical phenotypes, to determine if a single locus is responsible for all forms of the disease.

#### Urologic Diseases

• *Benign prostatic hyperplasia.* The reason for renewed growth of the prostate in adult males 30 and over remains unknown. The male sex hormone most associated with growth of sex accessory tissues, dihydrotestosterone (DHT), is probably not solely responsible for the renewed growth of the gland in

adulthood. It is clear that hormonal influences on this gland are mediated within the cell nucleus, in that both the hormone and its cell receptor migrate to the nucleus and bind to DNA.

While the research into the molecular bases of prostatic growth has been slow, a recent discovery increases the potential for significant progress. The observation was that circulating autoantibodies to human and rat androgen receptors are present in high amounts in the blood of some patients with prostate disease; thus, it should now be possible to use these reagents to isolate androgen receptors, prepare messenger RNA with the purified protein, and make cDNA probes. These are the reagents necessary to study the molecular biology and regulation of this receptor.

Another recent advance in this area which may link growth of the prostate in benign disease (BPH) to other proliferative diseases is a possible role for retinoic acid. It has been found that retinoic acid prevents estrogen-induced changes in the mouse anterior prostate gland as effectively as does an anti-estrogen. If retinoic acid plays a role in down-regulating factors which may participate in inducing abnormal prostatic growth, then a role for nutritional factors in BPH might be indicated.

#### *Hematologic Diseases*

• *The hope of future gene therapy: Planned alteration of the human hemoglobin gene.* A step that eventually may help in the treatment of sickle cell anemia and other anemias related to hemoglobin defects — some of the more frequent genetic disorders in man — has been taken by a team of Institute-supported researchers. They have succeeded in the preplanned alteration of a human gene that specifies the blueprint for hemoglobin, the oxygen-carrying protein of red blood cells. The hemoglobin gene that they altered is the one that is defective in Blacks with sickle cell anemia. It also is defective in some individuals of Mediterranean ancestry who have a different type of anemia called



*NIDDK-supported hematologic research has led to improved techniques for diagnosing hereditary anemias such as Cooley's anemia and sickle cell disease.*

Cooley's anemia. The investigators combined a portion of human DNA containing a selected region of the hemoglobin gene with the genetic material of cultured mammalian cells, using a microbial carrier. Since the cells in culture do not normally express hemoglobin genes, the appearance of hemoglobin synthesis by a significant proportion of these cells following insertion of the foreign DNA was a strong evidence for the success of this genetic manipulation. Coupled with the recently acquired ability to diagnose genetic hemoglobin diseases during prenatal development, the existence of this newly reported means to alter the nature and activity of the hemoglobin gene has the potential ultimately to provide specific therapy.

• *Treatment of aplastic anemia by immune suppression.* Acquired severe aplastic anemia is a rare, extremely serious, and often fatal disorder. It usually results from an unexplained and abrupt failure of the bone marrow to produce blood cells. Immunosuppressive agents enhance the success of bone marrow transplants. Some marrow transplant patients treated with the immunosuppressive agent



*NIDDK hematologic research is closely coordinated with other NIH blood disease programs. This research has increased basic knowledge about blood and has led to improved management of hematologic diseases.*

cyclophosphamide were found to have been cured, not by acceptance of the graft, but by the recovery of their own bone marrow. This unexpected result suggested that the aplastic anemia might be a disorder of the immune system rather than a failure of the bone marrow. It further points to the possibility of treating the disease by intensive immunosuppression. This postulate was confirmed in recent studies utilizing anti-thymocyte globulin, which acts to eliminate certain lymphoid populations of cells. Some of these patients have completely recovered. These studies have led to

the concept that there may be populations of lymphoid cells that suppress the normal growth of bone marrow in patients with aplastic anemia. These data also provide the opportunity to examine the mechanism of normal blood cell formation, and to understand and prevent or cure disorders that damage the blood cell formation system.

### **Summary and Conclusions**

The programs of the NIDDK encompass a multidisciplinary effort with major emphasis on basic biomedical and clinical research and research training. Institute efforts are planned and coordinated through both an extramural support program, which provides funding for research at universities, clinical facilities, and research institutions across the country and abroad, and an intramural component, which focuses on research conducted primarily within the NIDDK's laboratories and clinical facilities on the NIH campus and in Arizona.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance and fiscal, analytical, and review services to facilitate the research effort. Activities aimed at developing and sustaining linkages to the scientific and health-care communities also fall within the Institute's scope of responsibilities.

Historically, the concept of metabolism and metabolic diseases was a dominant theme in the overall scope of the Institute, and this has remained true to the present time. The closely related cluster of metabolism, nutrition, and endocrinology has provided a consistent focus of definition for the activities of the Institute, and these inevitably led to the study of immunological mechanisms underlying the diseases represented in Institute programs. The study of mechanisms has followed the needs of the research fields themselves, and has proceeded at all biological levels, molecular, cellular, tissue, organ, system, and organism in the environment.

## **National Institute of Diabetes and Digestive and Kidney Diseases Diabetes Research and Training Centers Program**

### **Introduction**

Diabetes Research and Training Centers (DRTC) grants were first awarded in September 1977 in conformity with the authorizing legislation (P.L. 93-354) and recommendations of the National Commission on Diabetes. At present there are seven DRTCs located at Albert Einstein Medical College/Montefiore Hospital (Bronx); University of Chicago/Michael Reese Hospital (Chicago); University of Indiana School of Medicine (Indianapolis); University of Virginia (Charlottesville); University of Michigan Medical School (Ann Arbor); Vanderbilt University (Nashville); and Washington University (St. Louis). Of the eight centers which were originally established, all have undergone at least one competitive renewal review, and seven have received continued funding.

The DRTCs are being evaluated continually through several varied but complementary processes, which include NIH peer review, the National Diabetes Advisory Board (NDAB), staff review of progress reports and staff visits to centers, special evaluation projects by Institute staff, annual meetings, and in-house evaluations by centers themselves. These approaches have been discussed in detail in previous reports. Only new efforts will be addressed in this report.

### **Center Features**

Excellence in biomedical research as evidenced by a substantial, high-quality base of NIH-funded investigators is the basic requirement for the establishment of a DRTC. The resources furnished by the center funding allow for enhancement of collaborative and multidisciplinary endeavors which span the spectrum of basic and clinical research to the transfer of new knowledge through training of primary care health professionals.

The DRTC funding allows for the establishment of shared resources (cores) for use by the investigators of the center, for a limited number of modest research projects (pilot and feasibility studies), and a small amount for program enrichment. The cores provide services to funded investigators, allowing for greater efficiency, better quality control, cost saving through bulk purchase, and fostering collaboration and multidisciplinary efforts. Funds for pilot and feasibility studies of modest amount and limited duration are provided for young investigators who do not yet have their own individual support, or established investigators from other fields who would like to use their expertise in diabetes research. A small amount of funding (less than 1 percent) is allowed for enhancement of the multidisciplinary environment through seminars and conferences, and through the exchange of information with consultants and lecturers from outside the center institution. The cores, pilot and feasibility studies, and the enrichment programs have been discussed in greater detail in previous reports.

The establishment of the DRTCs has provided the means for the consolidation of common interests and activities of basic and clinical scientists, practicing physicians, nurses, nutritionists, and other health care professionals in the diabetes area.

### **Special Evaluations Undertaken in FY 1986**

Evaluation is a process that is ongoing at all times. The evaluation process during FY 1985 was detailed in the report for that year. In the current fiscal year there is an ongoing evaluation by the NDAB in concert with a completed Institute staff effort.

The NDAB is currently preparing an update to the "Long-Range Plan to Combat Diabetes" proposed by the National Commission on Diabetes in 1976. This will include a very intensive look at the progress and accomplishments of the DRTCs,

the role of the DRTCs as a national resource, and recommendations for future directions. One meeting of the NDAB was held (April 21, 1986) at one of the centers so that the Board members could experience first-hand the functioning of a typical center. The NDAB expects to complete the new Long-Range Plan early in calendar year 1987.

In conjunction with the NDAB evaluation, NIDDK staff prepared an analysis of the pilot and feasibility program covering 1977 to 1986. The primary purpose of these small research projects is to allow new investigators and investigators from other disciplines to amass some data which would help them in preparing an application for regular NIH funding. Thus, a criterion which can be used in evaluating this program is to determine the proportion of recipients who remain in the diabetes area as funded investigators. This is the third analysis of the program which has addressed this point. In 1980, 37 percent of investigators who had received pilot and feasibility funding were principal investigators on NIH grants in the diabetes area; in 1983 this figure was 44 percent; in 1986, 39 percent. This does not include investigators who are co-principal investigators or who have funding from other peer-reviewed sources; in the 1986 study these figures were 8 and 18 percent, respectively. For comparison, the award rate for all new grant applications to the NIH in fiscal year 1984 was 25.5 percent.

Several general characteristics of the pilot and feasibility studies were also derived. Centers are able to award an average of 3.5 individual new projects per year; the average length for all projects was 2 years; and the average funding level per project per year has been \$18,300. More extensive analysis is available in a separate report prepared by Institute staff.

### Center Activities

There are basically two main thrusts for these centers: biomedical research and training and/or education of health care professionals involved in treatment and manage-

ment of diabetic persons. Although there is not necessarily a distinct division between these two activities, for the purposes of this report they will be considered separately.

### Biomedical Research

In previous years relatively detailed accounts of a major research effort at each of the centers has been presented. However, since this report is to be much more concise, only one example will be presented.

All currently available methods to treat insulin-dependent diabetes lead to imperfect metabolic control and none have been demonstrated conclusively to prevent the long-term complications of this disease in man. For over a decade a team of investigators at Washington University in St. Louis has been developing ways of isolating pancreatic islets from normal animals and transplanting these insulin-producing tissues into animals with diabetes. The long term goal of this research is to develop methods that might result in a permanent cure for insulin-dependent diabetes in man.

This group has made significant progress in islet transplantation during the past several years. A new technique for islet isolation led to demonstration that transplants of isolated islets within an inbred strain of rats would reverse experimentally induced diabetes to normal and would prevent or reverse early complications of diabetes involving the eye, kidney, and autonomic nervous system. However, two major barriers had to be overcome before islet transplantation could be attempted as a therapeutic approach to human diabetes; (1) prevention of rejection of the islet transplant without using immunosuppressive drugs (in experimental models it is now possible to overcome this problem with a variety of techniques); and (2) development of a method for islet isolation that would provide at least 25 percent of the islets from a single human donor pancreas. This amount is considered the minimum necessary to effect reversal of diabetes.

Recently a method has been developed which permits the isolation of up to 40 percent of the islets from a single human pancreas with a sufficient purity to transplant without immunosuppression into dogs and, in the future, man.

Meanwhile, the advances that have been made in overcoming these barriers have made it possible to initiate a first phase of human clinical trials in 1984 and 1985. The partially purified islet preparation was injected directly into the spleen of diabetic patients with stable kidney transplants who were being maintained on immunosuppressive therapy. The initial findings indicated that the islets would function after transplantation and the islet preparation was not toxic. Intrasplenic implants did not, however, result in survival of sufficient functional islet tissue to normalize glucose tolerance. Studies are now in preparation so that sufficient islet tissue can be transplanted directly into the liver via the portal vein during a relatively minor operative procedure so as to reverse insulin dependency in patients with type I diabetes.

When the first phase of the clinical trials is completed successfully, it will then be possible to initiate the second phase in which the donor islets will be treated to destroy the properties which cause rejection, and then to determine whether the islet grafts will survive over the long term without the use of immunosuppressive drugs.

Since 1978 the studies by this group of over 20 investigators from a variety of disciplines have led to over 37 major publications which have contributed significantly to progress in this very important effort to dramatically alter treatment of patients with insulin-dependent diabetes. Collaborative studies with investigators in other institutions are also under way.

### Training and Information Transfer

One of the major goals of the DRTCs is the training of practitioners of the health professions in diabetes and its management in the form of continuing education and information programs. These activities also include collaborations

and liaison with other Federal agencies and private organizations with interests and goals in other or similar activities relating to diabetes. The fiscal year 1985 report gave an overview of these activities with more detailed accounts of the most recent thrusts: inclusion of teaching skills in education programs, expanding target audiences, and transfer of new technology. Therefore, this report will address only two new items of interest and a brief overview of collaboration.

### **National Standards for Diabetes Patient Education**

An initiative of the NDAB in conjunction with several major diabetes groups (including the DRTCs) over the past 4 years was to develop national standards for diabetes patient education and, ultimately, to establish a process of recognition for programs that meet these standards. This Board initiative, including piloting the recognition process, was completed in December 1985. An indepth report will be published in the summer of 1986 in "The Diabetes Educator," the official journal of the American Association of Diabetes Educators. To bring this process to fruition in ensuring access to quality education services for people with diabetes, the National Coalition for Recognition of Diabetes Patient Education Programs (NACOR) was formed. Included on its board are representatives from most of the same major diabetes groups (including the DRTCs). The DRTCs collectively have developed over 35 state-of-the-art training programs of a wide variety for health professionals. Since these are offered on a regular basis or on request, they are potentially a major resource for health professionals seeking training in order to meet the criteria of the recognition process.

### **The 1985 DRTC Annual Education Meeting**

This meeting, held in December at the NIH, had as its focus national needs and future directions. Each center made a presentation on a general topic addressing this point

in relation to center accomplishments. These presentations are being published this spring as a supplement to "The Diabetes Educator."

### **Collaborations**

The DRTCs are expected to establish collaborations within their own group and with Federal and private agencies and organizations with missions relating to education and training in diabetes. Meeting this goal has become an important part of the activities of the centers. Active collaborations currently exist with Federal agencies (e.g., Centers for Disease Control and Indian Health Service); professional and voluntary health organizations (e.g., American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators); state and city health departments; local colleges; local hospitals; other voluntary organizations; and community health centers. Details of the nature of such collaborations were given in the FY 1985 report.

### **Summary**

This report briefly addresses the extent of fulfillment by the DRTCs of

the original goals set for them by the National Commission on Diabetes. Some new developments since the last report are described and indicate the great potential for the DRTCs as national resources in future progress in research and education in the diabetes area. The Department of Health and Human Services finds that the Diabetes Research and Training Centers are continuing to progress toward achievement of their objectives and sees their role as a national resource for progress in research and education in the diabetes area.

## **Digestive Diseases and Nutrition Centers Program**

In FY 1984, the NIDDK expanded the Digestive Diseases Research Center Program with the awards of six new center grants. In the following year, FY 1985, four additional research centers were established. The newly formed centers and the two previously established centers are listed in table 1 together with existing clinical nutrition research units (nutrition centers) supported by NIDDK.

Table 1  
**Research Centers Supported in FY 1985**

<b>Institution</b>	<b>Location</b>	<b>Principal Investigator</b>
<b>Digestive Diseases Research Centers</b>		
Harvard University	Boston, MA	William Silen, MD
New England Med Ctr	Boston, MA	Mark Donowitz, MD
University of Michigan	Ann Arbor, MI	Tadataka Yamada, MD
Mayo Foundation	Rochester, MN	Sidney Phillips, MD
University of Minnesota	St. Paul, MN	Joseph R. Bloomer, MD
University of Iowa	Iowa City, IA	James Christensen, MD
University of Colorado	Denver, CO	Francis R. Simon, MD
Albert Einstein College of Medicine	New York, NY	David Shafritz, MD
University of California	San Francisco, CA	Robert K. Ockner, MD
University of California	Torrance, CA	William J. Snape, MD
Yale University	New Haven, CT	James L. Boyer, MD
<b>Clinical Nutrition Research Units</b>		
Vanderbilt University	Nashville, TN	Harry L. Greene, MD
University of Wisconsin	Madison, WI	Alfred E. Harper, MD
University of Chicago	Chicago, IL	Irwin H. Rosenberg, MD
University of California	Davis, CA	Charles H. Halsted, MD
University of Washington	Seattle, WA	Edwin L. Bierman, MD



NIDDK provides support for research centers at institutions where there is an existing base of excellent biomedical research and where it can be demonstrated that the use of shared resources will lead to cooperative and collaborative research efforts. These efforts are to:

- (1) Lead to enhanced efficiency and low-cost routine services.
- (2) Lead to new cooperative and collaborative efforts among investigators.
- (3) Provide services and resources hitherto unavailable to investigators on a routine basis.
- (4) Expand the capabilities and potential for research accomplishments which will be greater than that possible by the support of individual projects.

## Digestive Diseases

### Biomedical Research Component

The biomedical research component at the digestive diseases centers focuses on one of several research areas such as liver disease; abnormal liver metabolism; problems related to liver transplantation; cholesterol gallstone disease; Crohn's disease and inflammatory bowel disease; normal and abnormal gastrointestinal motility; infectious diarrheal diseases; and absorption, secretion, and regulatory processes in the gastrointestinal tract. The research at all of the centers is directed towards enhancing the understanding and knowledge of digestive diseases thereby leading to improvement in the care of patients with these conditions.

### Biomedical Core Facilities

The biomedical research core at a digestive diseases center provides center investigators with shared resources to conduct biomedical research in an efficient and cost-effective manner. A list of these facilities is given in table 2. Among the benefits from these shared resources are:

- (1) A greater potential for collaboration.

- (2) The availability of expert consultation and use of state-of-the-art facilities.

- (3) A lower cost for services rendered.

- (4) The means to pursue limited developmental research.

For example, core facilities at the Harvard Digestive Diseases Center have been utilized by over 20 investigators for diverse projects in which a wide range of available methods have been employed including conventional transmission electron microscopy, freeze-fracture electron microscopy, light and electron microscopic immunocytochemistry, light and electron microscopic autoradiography, electron microscopic histochemistry, and electron microscopic lectin probe studies.

In other studies, investigators at this center are examining the luminal binding sites and the intracellular transport by suckling rat ileal epithelial cells of iodinated nerve growth factor and epidermal growth factor, exploiting the techniques of light and electron microscopic autoradiography.

At the Center for Gastroenterology Research on Absorptive and Secretory Processes at the New England Medical Center, studies are proceeding using the techniques of eukaryotic molecular biology. The very new field of intestinal peptides is of considerable interest because it has been found that some of those substances secreted in the gastrointestinal tract may be hormonally active in the central nervous system. Isolation of the gene encoding human pancreatic polypeptide has allowed researchers to construct a fusion gene containing the pancreatic polypeptide promoter linked to a bacterial marker gene, thus providing a path for the introduction of the gene into heterologous eukaryotic cells. The development of this procedure may provide the opportunity to study in a controlled manner several factors

that may affect the production of human pancreatic polypeptide.

At the liver center in San Francisco a core facility has been established to provide investigators with animal models of hepatitis B.

In recent years, striking progress has been made in understanding the molecular biology and pathogenesis of hepatitis B (HBV) through the use of animal models of this disease. However, since the existing models are confined to unusual animal species (ground squirrels, woodchucks, and ducks) requiring specialized facilities and expertise for maintenance, it is not practical for individual investigators to maintain colonies of such animals on their own. This core facility maintains a large colony of captive ground squirrels for research on matters relating to the replication of hepa-DNA-viruses and the pathogenesis of the diseases they cause. Recently, the scope of the core has been expanded to include the maintenance of a small number of susceptible ducklings for use in similar experiments. Ducklings are especially advantageous for hepa-DNA-virus research because of (1) the much shorter incubation period of DHBV infection — 3 weeks (vs. 2 to 3 months for the human, squirrel, and woodchuck viruses), and (2) the greater ease and lower cost of maintenance of infected ducklings.

### Pilot and Feasibility Studies

The center grant mechanism provides for the support of innovative research projects and few exploratory investigations which relate to the overall research focus at the center. These projects, as the name suggests, are supported to test new hypotheses, to provide opportunities for new collaborations, and to explore new methods or procedures as they apply to research problems in digestive diseases. Over ninety investigators are involved in pilot projects in the digestive diseases centers program. Examples of pilot projects approved for fiscal year 1985 are listed in table 3.



Table 2  
**Digestive Diseases Scientific Core Facilities**

University of Minnesota

Nutritional Assessment Core  
 Clinical Chemistry Core  
 Chromatography

University of Iowa

Neuroanatomy Core  
 Animal Maintenance Core  
 Data Management/Biostatistical Core  
 Motility Core

University of California, San Francisco

Editorial/Duplication Core  
 Animal Facility Core  
 Animal Models of Hepatitis B Core  
 Liver Cell Culture Core  
 Isolated Liver Perfusion Core  
 Microscopy Core  
 Mass Spectrometry Core  
 Spectrophotometry Core  
 Biomathematics Core  
 Protein/Peptide Analysis Core

University of North Carolina

Barrier Intact Animal Facility Core  
 Biostatistics Core

Harvard University

Electrophysiology Core  
 Membrane Preparation and Analysis Core  
 Morphology Core  
 Radioimmunoassay Core

University of California, Torrance

Immunology Core  
 Biochemistry of Inflammation Core  
 Morphology Core  
 Genetic Epidemiology Core  
 Human and Animal Research Core

Yale University

Hepatocyte Culture Core  
 Electron Microscope Core  
 Liver Biopsy Registry/Serum Bank  
 Transplantation Core

New England Medical Center

Intestinal Microbiology Core  
 Molecular Biology Core  
 Fluorescent Probe Core  
 Cell Culture Core

Mayo Foundation

Human and Animal Studies Core  
 Computer/Imaging Core  
 Radioimmunoassay Core  
 Morphology Core  
 Peptide Chemistry Core  
 Statistics/Epidemiology Core

Albert Einstein, College of Medicine

Special Animal Core  
 Morphology Core  
 Cell Culture Core  
 Protein Chemistry Core

University of Colorado

Liver Perfusion  
 Cell Culture Core  
 Lipid Metabolism Core  
 Bile Acid Determination and Mass  
 Spectrometry Core

University of Michigan

Molecular Biology Core  
 Biochemistry Core  
 Histochemistry Core  
 Radioimmunoassay Core  
 Tissue Culture Core

Table 3  
**Pilot Projects Approved for FY 1985**

Title	Investigator	Location
Connective Tissue Responses During Injury and Repair	J. Madera	Yale
Molecular Studies of the Ceruloplasmin Gene in Wilson's Disease	I. Sterlieb M. Stern	Albert Einstein
Cell Culture and Function of Intestinal Smooth Muscle	L. Miller	Mayo
Regulation of Gastrin in Peptic Ulcer Disease	J. Delvalle	Michigan
Mechanisms of Human Pigment Gallstone Formation	G. Everson	University of Colorado
Epidemiology of Inflammatory Bowel Disease	R. Sandler	University of North Carolina
Differentiation of Colonic Epithelial Cells in Experimental Colitis	K. Pang	University of California
Liver Preservation for Hepatic Transplantation	N. Ascher	University of Minnesota
Gastrointestinal Motility Changes in Response to Exercise	R. Summers	University of Iowa

### **Clinical Nutrition Research Units**

Advances in the knowledge of human biochemistry and physiology have placed clinical nutrition on a sound, scientific base. Many nutritional deficiency states, consequences of inborn errors of metabolism, and diet-related diseases are now understood, and may be treatable, or preventable. However, there remain many unanswered questions on the relationship of diet to health and disease, chronic diseases, and to aging.

Advances in research to help answer questions about nutrition and disease are derived from many disciplines (such as biochemistry, molecular biology, genetics, and

physiology) and medical specialties (such as internal medicine, pediatrics, and surgery). Nutrition science is interdisciplinary and complex and is dependent upon the close interaction among research, investigators, health service providers, and educators.

As a means of encouraging a multidisciplinary approach to clinical nutrition research, the NIH seeks to foster the development and operation of clinical nutrition research units (CNRU). Specific objectives of a CNRU are:

1. To create or strengthen foci in a biomedical research institution for multidisciplinary research in clinical nutrition in order to develop new knowledge about specific nutrients

in health throughout the life cycle, and in the prevention and treatment of disease.

2. To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition.

3. To enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU are:

1. Research with human subjects and populations;
2. Laboratory investigations;
3. Research training;
4. Shared facilities and research services;

5. Education programs for medical students, house staff, practicing physicians, and allied health personnel;

6. Research components of nutritional support services; and

7. Public information activities.

#### **CNRU Research Core Facilities**

Core facilities of CNRUs are developed to support research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged in order to increase knowledge concerning: (1) the function and requirements of nutrients, (2) the relationship of diet (and nutrients) to health and disease, and (3) the prevention and treatment of diseases as an outgrowth of nutrition research. The fundamental research supported by NIDDK generally has been nutrient-centered rather than focused on a particular disease, organ, or life cycle. In contrast, the clinical investigations usually concern problems interrelating nutritional status with the biochemical and physiological function of a cell population, organs, or the whole individual. A list of CNRU facilities is given in table 4.

Examples of the projects in the CNRUs which have been funded in FY 1985 are listed in table 5.

Table 4  
**Clinical Nutrition Research Units Scientific Core Facilities**

University of California, Davis	University of Washington
Vitamin and Mineral (Analysis) Core	Clinical Assays Core
Metabolism Core	
Cell Biology Core	
Food Biology Core	
Clinical Support Core	
University of Wisconsin	Vanderbilt University
Analytical Core	Nutritional Assessment Core
Clinical Core	Data Management Core
	Clinical Core
University of Chicago	
Vitamin Assay Core	
Nutritional Assessment Core	
Mineral/Trace Element Core	
Lipid/Lipoprotein Core	
Radioimmunoassay	

Table 5  
**Projects in the CNRUs Funded in FY 1985**

Title	Investigator	Location
The role of diet in reductive metabolism	Dr. Elmer	University of Washington
Proteolytic degradation of human milk lactoferrin in infants	Dr. Lonnerdal	University of California, Davis
Hypouricemia: A biochemical anomaly in total parenteral nutrition (TPN)	Dr. Sitrin	University of Chicago
Vitamin E, selenium and free radical scavenging systems	Dr. Asayama	Vanderbilt University

## Assessment

In 1984 the National Digestive Diseases Advisory Board held a workshop to explore possible mechanisms for evaluating and monitoring digestive diseases core research centers. This workshop was designed to draw on the experiences of other NIH center program activities to assure that the newly established research centers develop soundly. Suggested criteria and mechanisms for monitoring programmatic activity and suggested methods of obtaining evaluation information include the adoption of a standardized reporting method.

In October 1985, digestive diseases center directors met to consider and comment on a standardized format developed by the NIDDK for reporting information from the centers. A similar meeting of CNRU directors was held in January 1986 for the same purpose. This format is to be used in conjunction with the annual progress report required from each center. A draft of the format was reviewed by members of the subcommittee on centers of the National Digestive Diseases Advisory Board and the staff of the NIDDK, and the format was provisionally adopted for the 1986 reporting year. The information obtained from the annual reports will now provide useful information regarding programmatic aspects of these multifaceted research grants. It is anticipated that the reports will also provide useful information to peer review groups in the assessment of competitive renewal applications.

## Conclusion

The Department of Health and Human Services finds that the digestive diseases and nutrition centers are developing soundly and are taking steps to assure that assessment mechanisms and reporting procedures are in place. Progress made in the biomedical research base at the centers contributes to the fulfillment of the role of these centers. This role is to improve the understanding of the causes of digestive diseases, and of

nutritional metabolism in healthy and disease states—hereby leading to improved methods for early detection, diagnosis, and treatment of digestive diseases and nutritional disorders with consequent improved patient care and lower health care costs.

## The Biennial Report of the Director, National Institute of Neurological and Communicative Disorders and Stroke

### History

The following events represent milestones in the development of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

- August 15, 1950—The President signed P.L. 81-692, establishing the National Institute on Neurological Diseases and Blindness for research on neurological diseases (including epilepsy, cerebral palsy, and multiple sclerosis) and blindness.
- 1953-54—An intramural program of clinical investigation was initiated, including medical neurology, surgical neurology, and electroencephalography. Training programs in neurology and ophthalmology were initiated.
- 1956—The intramural clinical investigations program was expanded to include work in ophthalmology.
- 1957—Training programs in otolaryngology and pediatric neurology were begun.
- 1961—The first program projects and clinical research centers in stroke and communicative disorders were supported.
- 1962—Funds were appropriated for professional and technical information assistance. Training grants in neurosurgery and neuroradiology were initiated.
- 1966—The stroke research program was expanded; additional grants for clinical research centers were awarded. An antiepileptic drug testing program was begun.
- 1967—Vision outpatient research centers were established. A program of research in neural control mechanisms and prostheses was initiated.
- 1968—The blindness program of the Institute became the nucleus of

the new National Eye Institute (P.L. 90-489). The Institute was renamed the National Institute of Neurological Diseases and Stroke (P.L. 90-639).

- 1971—Programs in applied neurologic research (epilepsy, head injury), infectious disease, and biometry were added to the Collaborative and Field Research Division.
- 1973—Two new communicative disorders programs were begun with the establishment of a Section on Communicative Disorders, Collaborative and Field Research, and an intramural Laboratory of Neuro-otolaryngology.
- 1975—NINDS was renamed the National Institute of Neurological and Communicative Disorders and Stroke. NINCDS was reorganized into six major program units for (1) intramural research, (2) fundamental neurosciences, (3) communicative disorders, (4) neurological disorders, (5) stroke and trauma, and (6) extramural activities.
- 1976—Dr. D. Carleton Gajdusek, Chief, Laboratory of Central Nervous System Studies, was awarded the Nobel Prize in Medicine for work on typical slow viruses.
- 1978—NINCDS completed a comprehensive long-range plan for research in neurological and communicative disorders.
- 1982—The extramural Neurological Disorders Program was divided into two programs: the Convulsive, Developmental, and Neuromuscular Disorders Program; and the Demyelinating, Atrophic, and Dementing Disorders Program. This resulted in seven major program areas in the NINCDS.
- 1982—Dr. Murray Goldstein was appointed Director of the Institute.
- 1983—An independent study of research needs and opportunities in the neurosciences was mandated by Congress and completed by a panel of eminent neuroscientists and experts in the communicative sciences.
- 1983—Dr. Roscoe Brady, Chief of the Developmental and Metabolic Neurology Branch, was awarded the Lasker Prize for his research on lipid storage diseases, including Gaucher's disease.

## Introduction

The brain, boxed and cushioned by the cranium and cerebrospinal fluid, is a three-pound organ full of charged neurons sparking excitably with impulses that transmit chemical messages throughout the body—and represents the very essence of human life itself. The brain orchestrates behavior, movement, feeling, sensing. It controls all bodily functions.

For centuries man has been fascinated by the brain's mystery. While it is true that until quite recently understanding of the brain and the nervous system has been slow, fortunately scientists are now able to open the doors between the

known and the unknown with unprecedented frequency. The cycle of helplessness in the neurological sciences is being broken at last.

The programs of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) encompass 650 disorders that can devastate the lives of millions of Americans both young and old and impair the quality of life for them and their families. A person with Huntington's disease can live 20 years with increasing debility. People with Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and myasthenia gravis can live 5 or 10 or more distressful years. Persons with epilepsy, deafness, multiple sclerosis,



*The brain, a three-pound organ, is full of charged neurons sparking excitably with impulses that send chemical messages throughout the body. Here, a PET scan shows the brain in action. The light lavender area identifies accumulations of the neurotransmitter dopamine in the striatum of the brain.*

can live a normal lifetime, but their quality of life is significantly reduced.

In this era when people are taking more responsibility for their general health, it is interesting to note that these efforts probably have little impact on the incidence and extent of most neurological and communicative diseases, with the exception of some cases of stroke, head and spinal cord injuries, and hearing loss. Therefore, advances in the prevention, treatment, and cure of neurological and communicative disorders will depend heavily upon advances in basic and clinical research.

The chart on the last page of the NINCDS section of this report provides estimates on number of cases, their cost, and research dollars spent by the NINCDS for various neurological and communicative diseases. The many new methods and techniques that are being tried in basic and clinical research offer legitimate cause for excitement and hope. The opportunity for progress against these disorders has never been greater.

## **The NINCDS Structure and Programs**

### **Mission**

Since its creation 35 years ago, the Institute's mission has been directed toward finding the cause, prevention, diagnosis, and treatment of the neurological and communicative disorders and stroke. This is accomplished through extramural research and training support to talented scientists in research organizations all over the country and abroad, and through intramural studies conducted by the Institute's scientists working in its laboratories. More than 75 percent of the funds available to the NINCDS are allocated extramurally for investigator initiated research grants to investigators in public and private organizations such as universities, medical schools, hospitals, and research institutes.

### **Extramural Program**

The Institute's extramural program is divided into the following five program Divisions: Communicative Disorders; Convulsive, Developmental, and Neuromuscular Disorders; Demyelinating, Atrophic, and Dementing Disorders; Fundamental Neurosciences; Stroke and Trauma; and an administrative Division, the Extramural Activities Program, which provides administrative support and coordination for grants, contracts, and training activities.

### **Intramural Program**

The Institute's intramural program consists of 19 research branches and laboratories on the NIH campus and at Fort Detrick, Maryland, and Woods Hole, Massachusetts. The intramural program encompasses a wide range of studies involving basic and clinical research, and because of its stability, it is particularly able to take on the long-term research problems of fundamental importance to the neurological and communicative sciences.

### **Training and Development**

To help assure that future scientific expertise will be available for neurological and communicative research, the NINCDS participates in and supports a variety of research training and development award programs. These include:

- National Research Service Awards for 5-year Institutional Training Grants to public or private non-profit institutions principally for postdoctoral research training.

- National Research Service Awards for Individual Fellows, generally for 2 years of postdoctoral training.

- Research Career Development Awards of 5 years duration for those at the assistant or associate professor levels who need additional research experience in order to become established as independent scientists. The program provides primarily for career development in the basic sciences.

- NINCDS Teacher-Investigator Development Awards lasting 5 years to help young teacher/clinicians initiate their research careers. No new

awards of this type are being given, although current awards will be supported for the remainder of the award periods.

- NINCDS Clinical Investigator Development Awards lasting 3 to 5 years to prepare clinically trained persons for research and teaching careers in neurological and communicative medicine. These awards, unique to the NINCDS, replace the Teacher-Investigator Development Awards. Although the overall purpose is the same, the flexible time period and the opportunity for clinicians to take time out during their research training to meet advanced clinical requirements enables more clinicians to take advantage of the awards. These programs have already demonstrated their effectiveness in staffing clinical research neurological and communicative science programs throughout the country. They are receiving the highest priority for funding.

Through its training and development programs, the NINCDS will continue to provide for the core group of scientists needed to pursue neurological and communicative research. A cadre of basic and clinical scientists, well-trained in the newest technologies, must be ready to take up the challenges, participate in the excitement, and execute the techniques that will lead to improved health in the future.

### **Senator Jacob Javits Neuroscience Investigator Awards**

In October 1983, the 98th Congress created the Senator Jacob Javits Awards in the Neurosciences to honor the former Senator's energetic commitment to encouraging studies of the brain and central nervous system. The Javits awards are earned by scientists whose excellence, exceptional productivity, and cutting-edge research make them stand out from others in a pool of competing applicants. Up to 7 years of stable research support are provided. As of April 1986, 170 research scientists have been chosen to receive Javits awards. The NINCDS hopes to provide for 250 such awards to distinguished investigators in order to provide the stability of research support they require.



remote possibility but a realistic goal. A dramatic breakthrough was the discovery, by NINCDS grantees, of a genetic marker for Huntington's disease. This finding will soon make it possible to test people at risk for the disease before they have symptoms and to predict who will develop the disease and who will not. When the defective gene itself is isolated and its action understood, the next challenge will be to replace it with a correct copy. Equally significant are the potential applications of methods used in this research to other genetic neurological disorders. Already the discoverers of the Huntington's disease marker are using their newly developed genetic probes to locate gene markers for neurofibromatosis and tuberous sclerosis.

Meanwhile, identification of the genetic defect in Gaucher's disease, the most common lipid storage disorder, is about to yield a huge payoff for both diagnosis and treatment. NINCDS intramural scientists have isolated the pure form of the missing enzyme and, using recombinant DNA technology, are trying to produce large amounts of this enzyme to help the children who lack it. The scientists are also perfecting a strategy for delivering the enzyme to the specific cells where it is needed. The next goal will be gene replacement—inserting a correct copy in place of the defective gene in bone marrow and other tissues, so that the enzyme can be produced naturally in the body.

Other NINCDS-funded scientists are closing in on the genetic error that causes Duchenne muscular dystrophy, a progressive, muscle-wasting disease affecting one in 4,000 males. Using chemical markers called DNA probes, they have located the section of DNA that carries the defective gene. Although they have not yet found the exact site of the gene, they are close enough to use what they know for accurate detection of women who carry the gene and for prenatal diagnosis of the disease.



*An intramural scientist treats a young patient with Gaucher's disease, an inherited enzyme deficiency. The next frontier in treating this disease is gene replacement—substituting normal DNA for disease producing DNA.*

### **Viruses and the Nervous System**

Developments in molecular biology have converged with advances in neurovirology to generate new leads to be explored. Several examples are:

- *AIDS and the brain.* This year NINCDS scientists confirmed reports by other investigators that some 45 percent of AIDS patients develop AIDS encephalopathy, a destruction of brain tissue that leads to dementia. The Institute scientists also found that this brain disease is directly caused by the AIDS virus, rather than by another agent that takes advantage of the AIDS patient's depressed immune system. Even before someone exposed to AIDS develops clinical signs of the disease, they may have neurologic problems. This finding that the brain is a harboring site for the AIDS virus has disturbing implications for future treatment of AIDS. Should a vaccine or therapeutic drug be developed against the AIDS virus, it may be very hard to get either of them into the brain past a natural screen called the blood-brain barrier. More research is needed on how to

bypass this barrier to treat AIDS and other viral disorders lodged in the brain. How the AIDS virus interacts with the brain to cause such profound neurological dysfunction also needs to be clarified. Animal models are being used to study how AIDS suppresses the immune system and to test possible vaccines.

- *Slow viruses.* On the cutting edge of neurovirology are studies of slow or unconventional viruses—new kinds of infectious agents that may be involved in a number of neurologic disorders of unclear origins. These transmissible, virus-like agents can incubate in the body for years before making their effects known. They have been shown to cause a number of chronic, progressive central nervous system degenerations: Kuru and Creutzfeldt-Jakob disease in man, scrapie in sheep, and visna in goats. One NINCDS grantee has proposed that the cause of Creutzfeldt-Jakob disease is not a virus but a protein-containing particle, or "prion," that represents a new type of infectious agent.

### **Neurotransmitters and Movement Disorders**

Neurotransmitters are the chemicals that ferry messages from one nerve cell to another. Breakdowns in this messenger system have been implicated in a number of movement disorders, such as Parkinson's disease, myasthenia gravis, Tourette syndrome and other tic disorders, torsion and other dystonias, and the ataxias. The best hope for improving medical treatment of these disorders is basic research on neurotransmitter systems. If the current momentum of neurotransmitter research maintains its pace, this work is certain to generate information that can be applied to a wide range of movement and other disorders.

The PET scan is a valuable tool for analyzing neurotransmitter activity in the brain. For example, in studying Parkinson's disease, neuroscientists are using PET to try to understand why the drug L-dopa loses its effectiveness or does not work all

the time after 3 to 5 years. They suspect that the cell receptors for dopamine are not working properly, and PET is helping test this concept. Once the reason is known, they can work to improve drug treatment.

Tourette syndrome, characterized by involuntary muscle movements, uncontrollable vocal sounds, and inappropriate words, is suspected of being caused by an abnormality in the brain's neurotransmitter system. Neuroscientists are using PET scanners to try to identify the chemical defect. It is even possible that PET will reveal that stuttering, spasmodic dysphonia, and other speech defects are actually movement disorders traceable to a disruption in neurotransmission.

Knowledge of neurotransmitters will have important clinical implications for many neurological and communicative problems. For example, there is evidence associating epilepsy with changes in ion movement and imbalances in neurotransmitters. This clue has led scientists to test several new antiseizure compounds that act specifically on ionic movement and neural transmission.

### **Disorders of the Immune System—Myasthenia Gravis**

New opportunities for diagnosis and treatment are emerging from rapid advances in understanding the complex interactions between the nervous system and the immune system. Already benefiting from this knowledge are patients with the neuroimmune disorder myasthenia gravis, a crippling disease that affects at least 100,000 Americans.

Myasthenia gravis is a chronic neuromuscular disorder characterized by weakness and fatigue of the voluntary muscles. Recent findings indicate that the disease is caused by an autoimmune attack, in this case the body's immune system attacking its own cell receptors for the neurotransmitter acetylcholine, which transmits the signal that leads to muscle contraction. Clinicians have developed drugs and surgical procedures to control the symptoms, but continued treatment is necessary and sometimes has adverse side effects. More work is needed to search

for the cause of the autoimmune response, with the goal of "turning it off" with specific immunotherapy.

Some NINCDS grantees are trying to modify the protein structure of the cell receptors that are the targets of the autoimmune attack. The hope is that this change will "disguise" the receptors so that they are not interpreted as foreign invaders by the immune system. Then the myasthenic's body might stop making the receptor-destroying antibodies. Other Institute-funded scientists are experimenting with monoclonal antibodies. These laboratory-made substances are designed to affect only specific targets, and their purpose will be to control the cells that produce the receptors attacking antibodies without weakening the immune system itself. The same effect might also be induced by using the body's own suppressor cells, if a way can be found to do this.

### **The Role of Aging and Disease—Alzheimer's Disease**

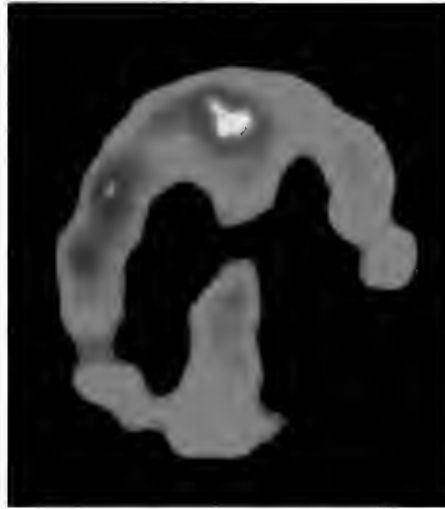
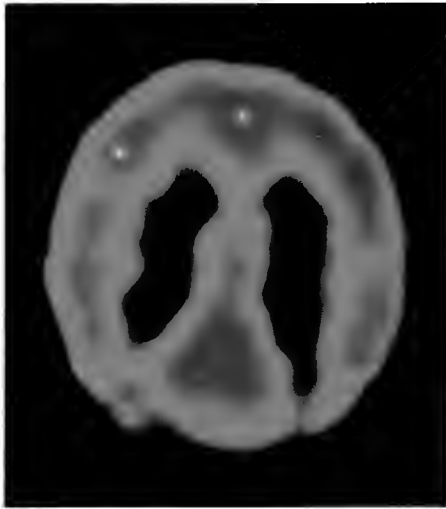
How aging affects the expression of various neurological and communicative disorders has long been of priority interest to the NINCDS. For example, Alzheimer's disease is now generally recognized as a neurological disease, not an inevitable result of old age. This knowledge has stimulated basic and clinical investigations designed to establish the biological basis for this degenerative brain disease, determine how it affects the brain's structure and chemistry, and test ways to alter its progressive course. Two of the best research leads right now are the identification of neurotransmitter defects in Alzheimer's affected brains and the search for a defective gene that causes familial Alzheimer's.

Within the last decade, it was discovered that Alzheimer's victims have abnormally low amounts of the neurotransmitter acetylcholine in their brain tissue. A specific area in the forebrain, the basal nucleus, was identified as the site where the damage to the nerve cells that manufacture acetylcholine was done. The basal nucleus has connections

to specific portions of the brain, the cortex and the hippocampus, where such higher functions as memory and thinking are controlled—functions so tragically deficient in Alzheimer's disease. The levels of other neurotransmitters, such as somatostatin, serotonin, norepinephrine, dopamine, and corticotrophin releasing factor (CRF), have also been found to be too low. These substances affect mood, memory, coordination, energy, and reflexes throughout the body. There may be a domino effect, where one deficient neurotransmitter results in a deficiency in another. Or there may be an unknown substance causing deficiencies among groups of different neurotransmitters. These are some of the theories being explored. Once these and other questions have been answered, neuroscientists hope to devise substances that will replenish neurotransmitter supplies and thereby prevent or lessen the effects of the disease.

According to data from various studies, particularly those of NINCDS intramural scientists, there is a genetic factor in Alzheimer's, with estimates of the frequency of this familial type of disease ranging from 20 to as high as 50 percent of the cases. It is also suspected that the Alzheimer's gene is autosomal dominant, carried by either the mother or father, which means that each child has a 50 percent chance of inheriting the gene if one parent carries it and a 75 percent chance if both parents carry it.

The most provocative finding of the last 5 years is the increasingly firm documentation that the principal risk factor for Alzheimer's disease is its expression in first or second degree relatives. Most recently, final results have been collected from the largest case-control study to date by a team of Institute and Italian scientists. A total of 116 patients were followed in seven locations in Italy, with the results showing that persons whose siblings have any form of dementia may be 11 times more likely to develop Alzheimer's disease. Secondary risk factors also identified were being a victim of head trauma with loss of



*The brains of Alzheimer's patients show distinctive patterns when imaged by PET. The scan of a normal brain is pictured at left. On the right, the scan of a 65-year-old woman with Alzheimer's disease, who could no longer set a table or make a bed, reveals loss of activity in the right hemisphere, where spatial relationships are controlled.*

consciousness within 10 years before the disease expresses itself and being born of a mother who was at least 40 years old at the time.

Efforts to collect information from families afflicted with Alzheimer's disease need to continue. The more parents, sisters, brothers, uncles, aunts, and cousins are studied, the more likely the chance of zeroing in on the defective gene.

#### **Problems in Communicating—Hearing Loss**

A communicative disorder can involve hearing loss, language difficulties, speech deficiencies and other problems—but the effect is the same. People who have any one of these disorders are hampered when they try to interact with others. Hearing loss, for example, has the effect of isolating millions of people because they cannot hear what is being said.

Scientists' understanding of why and how hearing becomes impaired is limited. To tackle the problem scientists are studying both normal and abnormal conditions of the ear and areas of the central nervous system involved with hearing. They are striving to discover how hearing takes place, why a loss of hearing-related nerve cells occurs, what

genetic and congenital factors influence ability to hear, and the role of aging, drugs, and noise on hearing.

Otitis media is a disorder of the middle ear that frequently produces a hearing loss in preschool children, and when severe, can impair their language development. Scientists are investigating whether the deficit

compromises healthy growth by starving auditory cells in the brain. They are also studying the effectiveness of surgery, as well as prevention, diagnosis, and other ways to treat this type of hearing defect.

Presbycusis is the name for hearing loss that frequently occurs in people over 65 years of age. Research evidence suggests that the inner ear and auditory nerve may simply wear out. The 30,000 microscopic hair cells in the inner ear that govern the ability to hear high-pitched sounds seem to be the most vulnerable in the auditory aging process. Common disorders of the elderly, such as heart disease and diabetes, have also been implicated, as have certain prescription drugs. Scientists are studying these and other possible causes, as well as the microscopic changes in the inner ear, and how age affects the transmission of nerve signals along the auditory pathways in the brain.

Impressive progress is being made in refining ways to improve hearing. The cochlear implant, a coin-sized receiver implanted in the ear to pick up electrical signals from a pocket-sized speech receiver worn on the body, enables the wearer to identify



*An NINCDS audiologist administers a test to a child with hearing loss.*

the presence of sound and some of its most basic characteristics. The multichannel devices now under development may permit someone who is profoundly deaf to comprehend speech. The second NINCDS funded clinical trial to test cochlear implants was awarded last year. Eventually, the deaf may be able to interpret the sound of the human voice as intelligible speech by means of computer-assisted speech processors. These devices electronically convert human speech into electrical signals, which then activate a cochlear implant. Also planned is a study to see if it is possible to design a special auditory prosthesis for people who have lost most or all of their auditory nerve.

### **Drug Development—Epilepsy**

The development of new drugs that will improve treatment of certain disorders is sometimes not pursued by industry because of marketplace considerations. This was the case with epilepsy in the 1960's. About 2.5 million Americans are affected by epilepsy, and at least 300,000 of them have seizures more than once a month. Most depend on drugs to control their seizures, but present day therapy is too often inadequate. For perhaps as many as 25 percent of them, the development of new drugs is their only hope for a better life. For this reason, the NINCDS Antiepileptic Drug Development Program (ADD) was created in 1973 to promote more effective, nontoxic drugs for people suffering from epileptic seizures.

The ADD program's Anticonvulsant Screening Project tests compounds sent from industrial and university labs around the world for effectiveness as anticonvulsants and for absence of neurotoxicity. This is done at no cost to the suppliers, who retain the patent rights to the compounds. Once a compound makes it through the screening process, the ADD's Toxicology Project tests its safety in animal models. The cost is shared with the pharmaceutical industry. The next step is to test the compound in humans to determine whether it treats the

disorder satisfactorily and is safe. Extensive clinical trials are conducted to evaluate the drug's long-term effects, with the costs also shared between public and private sectors.

To date about 10,500 compounds have been screened by the ADD program, and by FY 1987, clinical trials will be completed on 6 drugs being tested at nine institutions. During that fiscal year, there will also be ongoing studies of four drugs at five institutions. Since the NINCDS began supporting anti-epilepsy drug development in the 1970s, four drugs have been marketed and are now being widely used.

### **The Importance of Animal Models—Parkinson's Disease**

The serendipitous discovery that the effects of a toxin called 1-methyl-4-phenyl-tetrahydropyridine (MPTP) mimic the symptoms of Parkinson's disease has made it possible to construct an important animal model so that the nature of the disorder and better ways to treat it can be more thoroughly explored. Parkinson's disease victims suffer from a degeneration of the substantia nigra section of the brain, where neurons produce the vital neurotransmitter dopamine, essential for muscular coordination. Their symptoms are characterized by tremors, loss of spontaneous movement and facial expression, rigidity, and other types of movement disorders.

Because MPTP replicates the disease in an animal model, scientists have now been able to embark on a truly remarkable series of studies. They are implanting normal cells into impaired areas of the brain in the hope of reversing the damage—a technique that can have encouraging implications not only for parkinsonism, but for Alzheimer's disease and other maladies affecting particular parts of the brain.

Initial studies conducted before the MPTP discovery had shown that implanting dopamine-containing neurons experimentally alleviated abnormal motor behavior. Scientists later achieved similar results after

implanting fetal brain cells into models with MPTP-induced Parkinson's disease. Investigators are also testing other types of cell implants, such as using an animal model's own adrenal gland cells, which also produce dopamine.

A naturally occurring enzyme in the brain, monoamineoxidase type B (MAO-B), has been identified as causing MPTP to become toxic. One can speculate that in some patients Parkinson's disease also might be the result of exposure to environmental toxins that are rendered harmful by this same enzyme once they enter the brain.

There may be several approaches to preventing the onset or halting the progress of the degenerative process of parkinsonism, such as using drugs to inhibit the brain's MAO-B enzyme from interacting with certain substances to form toxins, or to block the uptake mechanism for dopamine to prevent accumulation of toxic substances in the dopamine neurons. There is some evidence that smokers are less likely to have Parkinson's disease. This suggests that some substance in tobacco may have a protective effect on the degenerative process, perhaps by interfering with the uptake mechanism or metabolism of a toxic substance commonly inhaled or ingested with food.

These areas of exploration—brain cell implants to restore normal function, the degenerative process of parkinsonism, and drugs to alleviate or treat symptoms—are progressing rapidly. Tremendous improvements may be expected within the lifetime of most Parkinson's patients.

### **The Importance of Clinical Trials—Stroke**

Clinical trials in the neurological and communicative sciences play an essential role in evaluating drugs, neural prostheses and certain surgical procedures, such as surgery performed as a preventive measure against stroke. The recently completed evaluation of the extracranial/intracranial (EC/IC) bypass operation, a stroke prevention procedure, was made possible by a well-conducted clinical trial that provided

a wealth of solid information for physicians to consider.

The EC/IC bypass has been performed for almost 20 years. It replenishes blood supply to the brain by using a scalp artery to reroute blood past certain narrowed arteries clogged with a buildup of fatty substances that block the flow of nourishing oxygen and nutrients the brain cells need to survive. Several thousand of these operations are performed in the United States every year at an estimated cost of \$15,000 per operation.

The outcome of the clinical trial was dramatic. This 8-year international study found that the operation is less effective in preventing stroke than taking aspirin and controlling high blood pressure. The impact of these results promises to be significant for the well-being of stroke-prone patients and for lowering national health costs by curtailing this type of surgery. In addition, a wealth of data on stroke was accumulated as a result of the clinical trial. Subsequent analyses of the information could prove to be as valuable as the primary study itself and might point to the need for other clinical trials.

One possibility is a study of the third most frequently performed operation in the United States—the carotid endarterectomy. About 100,000 of these operations take place annually. The purpose of the procedure is the same as the EC/IC bypass—to ward off stroke by increasing blood flow to the brain, this time by removing partially or fully occluded portions of the carotid artery in the neck.

Plans for a NINCDS-supported clinical trial to study the effectiveness of the carotid endarterectomy operation are now being evaluated. Amid reports of surgical complications, even death, there is also some evidence that, as was the case with the EC/IC procedure, medical care alone may reduce stroke incidence without the added risk of carotid surgery.

### Neuroscience in Space

In addition to exploring how the brain functions on earth, neuro-

scientists participating in the U.S. space medicine program are searching for answers about how the brain functions during space flight. Although fewer than 250 people have undertaken space flight so far, it is expected that future missions will involve much broader segments of the American population whose health may be affected by a changed environment.

Space motion sickness as a reaction to weightlessness is a neurophysiological problem resulting from conflicting signals sent by the balance organs of the inner ear, the eyes, and the muscle sensors. About half of all astronauts have experienced lethargy and vomiting for 3 or 4 days after their first exposure to weightlessness. Before measures can be taken to reduce or prevent space motion sickness, much more must be learned about the underlying neurophysiological changes. Neuroscientists believe that these symptoms may arise from changes in the fluid compartments of the brain, a hypothesis that needs to be explored. Another aspect of this problem is the effect that changes in the brain's fluid compartments may have on cognitive functions such as problem-solving and alert responsiveness.

Also on the agenda for space neuroscience is basic work on the perception of position in space and how people orient their bodies in a zero gravity environment. Without normal sensory inputs to the part of the inner ear that controls balance, moving around becomes an exercise in disorientation. Current studies on the structure and function of the ear's balancing system in health and disease are expected to provide information relevant to helping people maintain their sense of equilibrium when they are in a weightless condition.

### Hope for the Future

To know how to prevent the neurological and communicative diseases or halt them means that neurological and communicative scientists must first rely on basic research efforts. How chemicals modify and regulate the functions of the brain, how nerve cells are formed, do their job, and die, and what

alterations diseases make in that process are increasingly being understood. Then techniques such as gene therapy, monoclonal antibodies, vaccines or drugs, and surgery can be activated in the fight against disease.

Already clinicians are able to help ease the symptoms of certain maladies. New therapies, such as improved drugs, are being devised for disorders such as epilepsy, otitis media, and Parkinson's disease, while other therapies are being discarded in favor of safer alternatives. There is new hope that the effect of some diseases can be slowed down. One example is multiple sclerosis, which frequently takes the form of repeated expressions of the disorder, followed by remissions, with each expression period causing additional loss of function of the central nervous system. There are now some preliminary findings that the drug Copolymer I reduces the frequency of these attacks and lessens the degree of disability.

The 1980s are exciting times for neurological and communicative scientists. In so many areas they find themselves on the threshold of revelations that promise relief from deadly, crippling diseases and their consequences. Each advance in basic and clinical research has a spillover effect that covers a multitude of diseases. The new technologies enable scientists to draw conclusions from a broad spectrum of information never before available. Recent knowledge of how the brain works and the ways diseases can cause it to malfunction is now at a point where scientists may soon divert the destructive course of neurological and communicative disorders.

The cadre of needed basic and clinical scientists is in place; the fundamental reorganization of our understanding of how the neurological and communicative systems function is occurring; research methodologies are available for studying etiology and pathogenesis. The decade of brain research has started with the promise that there is hope through research for preventing or treating the destruction of the brain.



# The Biennial Report of the Director, National Institute of Allergy and Infectious Diseases

## History

The following events represent milestones in the development of the National Institute of Allergy and Infectious Diseases (NIAID).

- 1887—The Laboratory of Hygiene (a bacteriological laboratory, which was the forerunner of the NIAID, and indeed of all of the NIH) was established.
- 1948—The National Microbiological Institute was established. The Rocky Mountain Laboratory and the Biologics Control Laboratory, both dating back to 1902, were incorporated into the new Institute, together with the Division of Infectious Diseases and the Division of Tropical Diseases of NIH.
- 1951—An Institute-supported grants program was initiated, and a branch was established to administer research, training, and fellowship grants.
- 1955—The National Microbiological Institute became the National Institute of Allergy and Infectious Diseases.
- 1962—A collaborative research program funded mainly by contracts was established to coordinate nationwide projects on infectious diseases, vaccine development, transplantation immunology, research reagents, and antiviral substances.
- 1977—The administration of extramural research was reorganized into the: Microbiology and Infectious Diseases Program; Immunology, Allergic, and Immunologic Diseases Program; and Extramural Activities Program.
- 1978—The first maximum containment facility (P4) for recombinant DNA research was opened in Frederick, Maryland. Centers were created for interdisciplinary research on immunologic diseases.

• 1979—The Office of Recombinant DNA Activities was transferred from the National Institute of General Medical Sciences to NIAID.

• 1984—Dr. Anthony S. Fauci was appointed Director of the Institute.

## Introduction

The general purpose of the National Institute of Allergy and Infectious Diseases (NIAID), as stated in P.L. 99-158, is the conduct and support of research, training, health information dissemination, and other programs with respect to allergic and immunologic diseases and disorders and infectious diseases.

To accomplish Institute goals, the NIAID conducts basic and clinical research in its laboratories in Bethesda and Frederick, Maryland, and Hamilton, Montana, and awards grants and contracts to support research and research training in institutions throughout the United States. The Institute supports basic research in the disciplines of virology, bacteriology, parasitology, mycology, molecular biology, immunobiology, immunochemistry, immunoregulation, immunogenetics, transplantation biology, and immunopathology. The NIAID has the lead responsibility for conducting and supporting research on the immune system, only recently recognized as a distinct organ system. Applied and clinical investigations, including clinical trials of preventive and therapeutic agents, are supported in the areas of infectious diseases, allergy, and clinical immunology.

The ultimate goal of all the Institute's research programs is to improve methods for the prevention, diagnosis, and treatment of infectious and immune-mediated diseases. NIAID investigators are devising new approaches to combat infectious agents and are uncovering new ways to enhance the protective powers of the immune system and to diminish its destructive effects or restore deficiencies when it malfunctions. Their efforts are facilitated by advances in molecular biology, which now permit a better understanding of microorganisms and cells at the fundamental molecular level.

## Research Activities of the Institute

### Vaccine Development

Vaccines are among the most effective means of disease prevention. Diseases that ravaged mankind in the past including smallpox, polio, whooping cough, and measles, have been completely or virtually eliminated from the United States by immunization.

### Meningitis

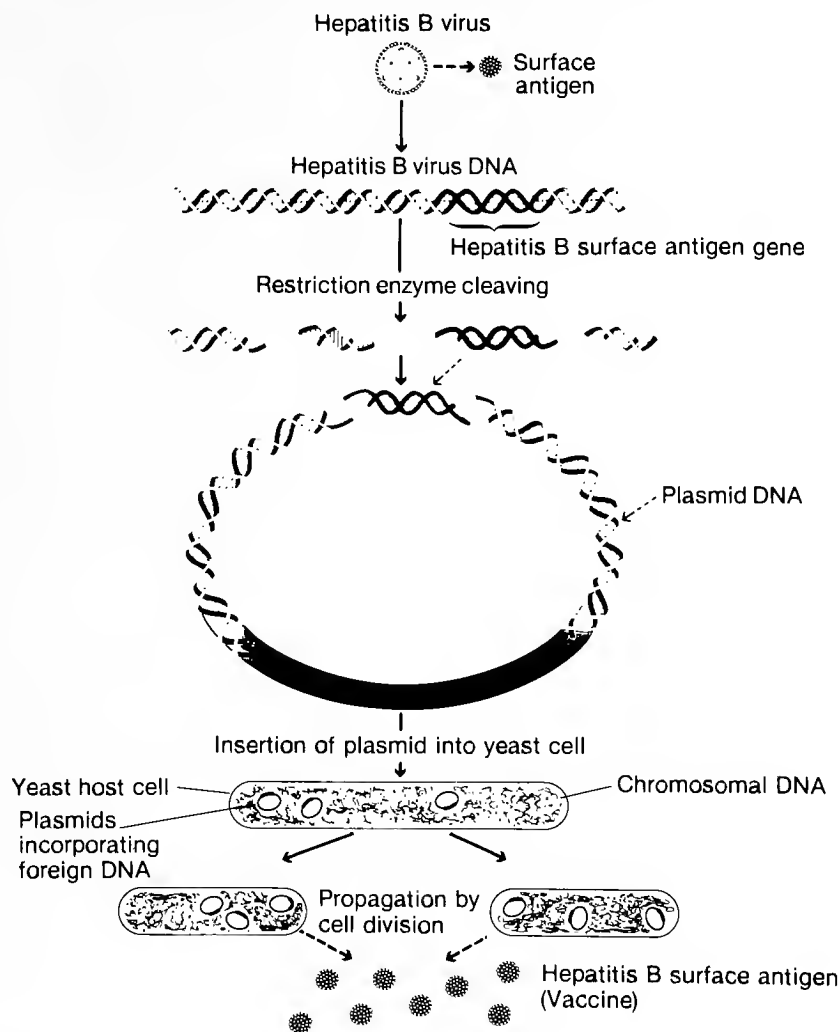
A polysaccharide vaccine for the prevention of the most important cause of bacterial meningitis in children, *Haemophilus influenzae*, type b, was licensed in 1985 for use in children 2 years of age or older. With NIAID funding, a modification of this vaccine (protein-polysaccharide conjugate) designed to make it immunogenic in younger children is being tested in high-risk Eskimo children in Alaska.

### Hepatitis

About 200,000 cases of hepatitis B virus (HBV) infection are estimated to occur yearly in the United States. In addition, there are at least 800,000 chronic carriers in the United States and 200 million worldwide. A high percentage of people who are chronic carriers of the virus develop cirrhosis of the liver. They are also at increased risk for primary hepatocellular carcinoma (PHC), a form of liver cancer. An estimated 250,000 people worldwide develop PHC each year. Although there is an effective HBV vaccine available, it is not widely used. Using recombinant DNA and other new technologies, investigators have developed second-generation, less expensive HBV vaccines. The licensed plasma-derived vaccine consists of a surface antigen (S) from HBV. NIAID grantees have recently identified another protein, designated PreS; whether its presence together with the S antigen in a vaccine will provide better protection than S alone is under study.



## GENE CLONING FOR THE PRODUCTION OF HEPATITIS B VACCINE



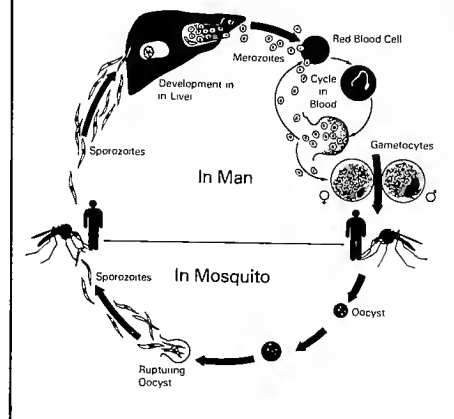
Gene cloning for the production of hepatitis B vaccine.



An NIAID intramural program scientist administering nose drops containing influenza vaccine made from live, attenuated virus.

### Influenza

Influenza continues to be the most serious infectious disease in the United States, affecting millions of individuals every year. Live attenuated influenza virus vaccines (produced through the use of live, weakened viruses), administered intranasally, are being tested in young children and in adults with cardiopulmonary disease for safety and efficacy by NIAID intramural scientists and contractors.



Malaria life cycle.

### Malaria

Approximately 300 million people in the world today have malaria. Researchers supported by the NIAID have been successful in developing candidate vaccines against the most important parasite causing malaria, *Plasmodium falciparum*; the vaccines will be tested during 1986 for safety and antigenicity in human volunteers. These vaccines contain forms of a protein found on the surface of the sporozoite stage of the parasite. Another approach involves the merozoite stage of the parasite, which forms in the red blood cells (RBCs). A protein on the surface of the merozoite has been shown to bind to a specific receptor on the surface of red blood cells. Further characterization of this antigen and others from the merozoite and gametocyte stages of the parasite may lead to still other malaria vaccine candidates.

### Cystic Fibrosis

Cystic fibrosis (CF) is one of the most common genetic diseases. Persons suffering from CF experience an array of serious health problems and have shortened lifespans because of chronic lung and airway damage caused by infections, especially by the bacterium, *Pseudomonas aeruginosa*. Research is under way to evaluate methods to protect against *Pseudomonas* lung infections. A capsular complex sugar mucoid exopolysaccharide antigen found in a majority of *Pseudomonas* strains infecting CF patients was

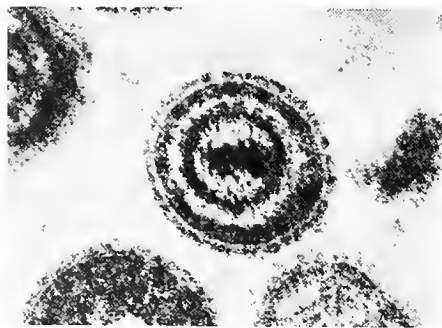
demonstrated in a guinea pig model to be protective against lung infection, by both active and passive immunization.

#### *Infantile Diarrhea*

Rotaviruses are the most important cause of severe infantile diarrhea throughout the world. Field trials of two live rotavirus vaccines derived from calf or rhesus monkey viruses are under way. The calf strain has protected 88 percent of vaccinated Finnish children against severe rotavirus diarrhea. The rhesus strain, developed at the NIAID, has shown similar protective efficacy in preliminary results from a trial in Maryland infants. A direct comparison of the rhesus and calf strain vaccines is currently under way in Navaho Indian infants in Arizona. Recombinant DNA technology has resulted in the production of alternate and hopefully more protective vaccine candidates, not yet tested in man, that contain antigens located on the coat of human rotaviruses.

#### *Chickenpox*

Varicella (chickenpox), a highly contagious viral disease of children, is not usually associated with serious sequelae or death. However, it is a major problem in immunosuppressed children such as those with acute leukemia who are undergoing chemotherapy. The NIAID evaluated an attenuated varicella vaccine in leukemic children, and the results demonstrated that the vaccine is safe and effective. Licensing by the FDA is expected in 1986.



*Varicella virus, the cause of chickenpox.*

#### *Respiratory Infections*

NIAID-supported investigators have succeeded in mapping and characterizing the genes of respiratory syncytial virus (RSV), an important cause of respiratory infections in children. RSV has four surface proteins. Two of these, the G protein and the F protein, are thought to be important because, like the influenza virus hemagglutinin, they perform important functions in virus replication. Studies are in progress to develop vaccines from these proteins.

#### *Hepatitis A Virus*

NIAID intramural scientists have grown hepatitis A virus (HAV) in tissue culture systems and produced live attenuated virus strains. Vaccines made from these strains were tested for safety in animal models. NIAID intramural scientists have also cloned the entire genome of HAV and sequenced it. The regions of the genome encoding the surface antigens have been identified, and proteins produced by expression of these genes are being explored as potential vaccines. In addition, synthetic peptides have been shown to be antigenic, and their ability to protect against infection and disease will be studied.

#### *Spotted Fever and Lyme Disease*

Molecular approaches toward understanding the bacteria causing Rocky Mountain spotted fever, *Rickettsia rickettsii*, and Lyme disease, *Borrelia burgdorferi* (named after the NIAID intramural scientist, Dr. Willy Burgdorfer, who identified the agent), have been initiated. In studies of *B. burgdorferi*, the genes coding for the two major outer membrane proteins have been cloned and characterized. This is an important step towards the development of vaccines against these medically important diseases.

#### *Rabies*

The genome of the rabies virus has been isolated, cloned as complementary DNA, sequenced, and mapped for the gene encoding the surface glycoprotein (gp). The gp gene has been inserted into vaccinia virus and the resulting recombinant product has been shown to protect foxes, skunks, and raccoons against rabies

when fed in bait. This type of vaccine has potential for developing countries where rabies is a serious endemic problem.

#### *Sexually Transmitted Diseases*

Sexually transmitted diseases (STDs) are a major problem throughout the world. In the United States, approximately 900,000 cases of gonorrhea and 70,000 cases of syphilis were reported in 1984. Of greater public health importance, however, are the estimated 5,000,000 chlamydial infections and 500,000 new cases of genital herpes. Pelvic inflammatory disease (PID) is the most serious and costly complication of STDs affecting women. Each year more than one million women in the U.S. experience an episode of PID. A recent study in the *Journal of the American Medical Association* estimated that total costs of PID exceeded \$2.6 billion in 1984. Nearly 40,000 women annually are rendered sterile as a result of PID.

#### *Syphilis*

Monoclonal antibodies specific for antigens of the spirochete causing syphilis have been developed. This monoclonal material, coupled to a fluorescent dye, has been used to detect the presence of the spirochete in clinical specimens from syphilitic patients. This method may provide a more convenient and accurate diagnosis of early syphilis than do current methods. Expanded studies will determine whether this new test should be recommended for general use.

#### *Chlamydial Infections*

Genital infection with *Chlamydia trachomatis* is now the most common bacterial sexually transmitted disease in the United States. Recent studies within the NIAID intramural program resulted in new rapid diagnostic tests that can identify *C. trachomatis* infections in both symptomatic and asymptomatic patients. It is now clear that there is a significant adverse association between *C. trachomatis* infection and outcome of pregnancy, with an increased incidence of spontaneous abortion, premature labor, low birth weight infants, and chlamydial pneumonitis in children born to infected mothers.

Studies are in progress to better characterize the molecular constituents of chlamydial membrane proteins, which would improve treatment and control of this infection and accelerate vaccine development.

### *Gonorrhea*

Gonorrhea remains a major problem in the United States and throughout the world. Recent investigations by NIAID scientists have focused on the mechanism by which the infectious agent, *Neisseria gonorrhoeae*, invades the host. It has been shown that *N. gonorrhoeae* contains hair-like projections called pili, which are probably important in the development of the disease. The gene sequences controlling pilin, a constituent of mature pili, have been determined. These basic studies may have important implications for future therapy or prevention of infection. In addition, NIAID-supported extramural investigators have recently characterized two new proteins that show potential for future development of a vaccine against gonorrhea. One is an outer membrane protein antigen, termed H-8 antigen, that appears to be common to all pathogenic strains of *Neisseria*. The other is a newly discovered iron-regulated protein that elicits an antibody found in all patients with naturally acquired infections.

### *Genital Herpes*

Genital herpes can be a physically and psychologically debilitating infection. NIAID intramural scientists were among the first to report an effective means of suppressing recurrences of genital herpes with the drug, acyclovir. Transmission of herpes from mother to infant at birth is a serious threat to the newborn. New information on the prophylactic treatment of neonates with acyclovir indicates that, in cases where infectious virus has been detected in vaginal secretions, neonatal herpes may be prevented if therapy is instituted promptly after delivery. Scientists are developing candidate vaccines for herpes using a variety of approaches. Intramural investigators prepared one such vaccine by inserting herpesvirus genes

into vaccinia virus. This experimental vaccine protected mice against challenge with lethal doses of herpesvirus.

### *Genital Warts*

Evaluation of interferon treatment for condyloma acuminata (genital warts, caused by papilloma viruses) is progressing. An NIAID-supported, placebo-controlled, clinical trial tested three different interferon preparations administered directly into the wart on the assumption that this would be the best approach for detecting activity but not necessarily the ideal route of administration. A follow-up protocol is currently under way in which several alpha interferon preparations are being compared in a placebo-controlled study utilizing parenteral administration.

### **Other Infectious Diseases**

#### *Respiratory Syncytial Virus*

The search for effective antiviral drugs for the treatment of respiratory syncytial virus (RSV) infections is progressing. A family of compounds (amidines), which inhibit specific reactions in the maturation of RSV, is under study. Encouraging results also have been obtained with an antiviral drug (ribavirin) administered via aerosol; it has been shown to be effective in the treatment of severe RSV infections of children.

#### *Hepatitis Delta Virus*

Hepatitis delta virus (HDV) is a recently identified defective virus that may infect people who have acute or chronic hepatitis B virus (HBV) infections. Severe liver disease may result, often leading to death. Using recombinant DNA technology scientists have now cloned the complete genome of HDV and sequenced it. This information, along with other characteristics recently discovered, should enhance the development of prophylactic measures.

#### *Non-A, Non-B Hepatitis*

Non-A, non-B hepatitis (NANB) accounts for about 90 percent of the transfusion-related hepatitis and 20 percent of the general hepatitis seen worldwide. NANB infections, like those of HBV, can progress to chronicity and cirrhosis. The chim-

panzee is the only available animal model for studying this disease, since NANB virus(es) are not known to infect other animal species. Recently, NIAID intramural scientists have shown that one type of NANB virus is a lipid-enveloped virus with an RNA genome. Work by NIAID scientists indicates that treatment of plasma derivatives with lipid-destroying agents may prove useful for eliminating this type of NANB. A monoclonal antibody has been developed that detects this type of NANB virus; it is being used to study NANB infection in the chimpanzee and in human samples.

#### *Laryngeal Papillomatosis*

Laryngeal papillomatosis (warts in the larynx caused by papilloma viruses) is quite rare, but when it occurs in children it is frequently associated with genital warts in the mother, suggesting acquisition during the birth process. The warty growths in the larynx can obstruct the airway, and surgery has been the only available treatment. With aggressive disease, surgery must be repeated as frequently as every few weeks. The NIAID is currently conducting a large controlled clinical trial of interferon treatment of children with laryngeal papillomatosis.

#### *Toxic Shock Syndrome*

Studies of toxic shock syndrome (TSS) continue to examine the role of toxins produced by the bacterium, *Staphylococcus aureus*. Strains of *S. aureus* isolated from patients with TSS produce a characteristic protein. This toxic shock marker protein (TSMP) has been purified and found to be a potent inducer of interleukin-1 (IL-1) production by human monocytes. Many features of TSS suggest that induction of IL-1 by TSMP *in vivo* may play a central role in this disease.

#### *Epstein-Barr Virus*

Epstein-Barr virus (EBV) is a ubiquitous herpesvirus associated with several lymphoproliferative diseases of man, the most notable of which is infectious mononucleosis. EBV has a latent state that allows the virus to endure for the life of the individual. Recently, using recombinant DNA

techniques, scientists have cloned and analyzed most of the DNA of EBV. The viral capsid antigen (VCA) of EBV has been expressed in cells transfected with viral DNA; VCA is expressed on the membrane of infected cells and is important for the attachment and penetration of the virus into cells. Use of highly specific monoclonal antibodies has revealed the presence of previously unrecognized antigens of EBV in the nucleus of latently infected lymphocytes. Clinical trials are under way using acyclovir and 9-1,3 Dihydroxy-2-Propoxymethyl Guanine (DHPG) to treat EBV infections.

#### *Fungal Infections*

A mouse animal model has been developed to study the pathogenesis and potential methods of control of the fungus, *Cryptococcus neoformans*. Investigators are looking at the role of macrophages and natural killer cells in the initial clearance from the lungs of intratracheally or intravenously administered *C. neoformans*. Macrophages appear to play a critical role in clearing intratracheally administered cells, while natural killer cells are more important against the intravenously administered cells.

The occurrence of deep-seated fungal infections appears to be increasing, especially in debilitated patients who are immunosuppressed from cancer therapy or from other treatment modalities. Standard treatment with the antifungal drug, Amphotericin B, requires hospitalization for intravenous administration and close monitoring for serious side effects such as impaired kidney function. Improved therapy for this group of infectious diseases is sorely needed. Controlled clinical studies are under way to evaluate a novel antifungal agent, Fluconazole. This new agent has been shown safe and effective in animal models and can be given orally to patients on an outpatient basis. It appears to be devoid of any serious side effects. During the next 2 years, clinical studies are planned in patients with systemic histoplasmosis, blastomycosis, coccidioidomycosis and candidiasis.

#### *Leprosy*

NIAID-supported investigators have isolated and characterized antigens specific to *Mycobacterium leprae*, the organism responsible for causing leprosy. Serodiagnostic tests were developed using these specific antigens and the tests were used to detect *M. leprae*-specific antibody in sera from leprosy patients. These tests are being used to detect early stage leprosy before symptoms appear and are particularly useful in monitoring close contacts of persons with leprosy. During treatment, these tests are used to monitor the antibody level in patients' serum. It has been shown that a decrease in antibody level correlates with the killing and disappearance of leprosy bacilli in these patients.

#### *African Sleeping Sickness*

African sleeping sickness is a tropical disease caused by a trypanosome, transmitted by the bite of the tsetse fly. Invasion of the brain results in encephalitis leading to somnolence, coma, and death. Suramin is an effective drug if used prior to invasion of brain tissue by the parasite. Melarsoprol is effective in the brain but is very toxic. Studies of difluoromethyl-ornithine (DFMO) have shown it to be curative in mice, and trials in humans in Africa have shown promising preliminary results. DFMO tested in combination with suramin was found to exert a synergistic effect, resulting in an extremely high cure rate. A less toxic analog of DFMO has been synthesized and is being studied.

#### *Filariasis*

Filariasis occurs in the tropics in several forms, the best known being elephantiasis and onchocerciasis (river blindness). The various types of filariasis are diagnosed by observation of the larval state (the microfilariae) in blood or tissue. It is often difficult to identify species, especially in the mosquito where human parasites may be mixed with numerous animal filariae. Recently, scientists have used molecular biological techniques to develop a better diagnostic test. A genomic library of one parasite species has been screened to detect clones con-

taining DNA sequences that are highly repeated within the parasite genome and do not cross-hybridize with DNA of other species. One clone was detected that is highly specific and sensitive. It correctly identifies infective larvae-containing mosquitoes and does not react with mosquitoes containing larvae of other species. The diagnostic potential of this system will now be field tested. NIAID is also participating in clinical trials of Ivermectin and Benzthiazole in patients with filariasis in India and Ghana.

#### *Scrapie*

Scrapie is a slow virus that causes an infection in sheep and goats similar to slow virus diseases such as Creutzfeldt-Jakob disease and Kuru in man. The virus is markedly resistant to agents that inactivate most viruses, and the disease causes no detectable host immune response. The intimate association of scrapie with host protein may account for many of its unusual features. NIAID intramural scientists have established high-titered, scrapie-infected, tissue culture cell lines and cloned the scrapie prion protein gene. These studies open important areas for investigation of the pathophysiology of slow virus infections, which may have relevance to Alzheimer's disease.

#### *Immunology*

While all NIH Institutes support immunology research, the NIAID is the lead Institute for basic studies of the immune system, which is now recognized to be a discrete organ system of the body whose proper functioning is essential to good health. The development of agents and procedures to defend against attacks on the immune system and to restore damaged immune function are extremely important goals.

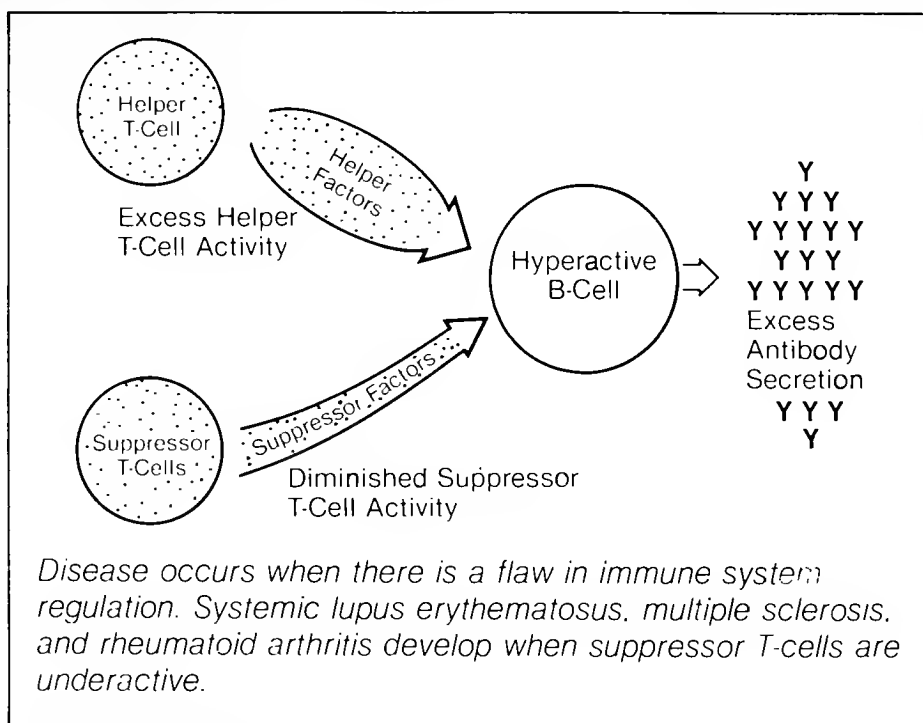
Now that scientists have the capability to clone individual immunocompetent cells, particularly specific subpopulations of T lymphocytes, they can conduct detailed studies of T-cell molecular structure and of the functions of surface molecules involved in the recognition of foreign components and the

subsequent activation of the immune system. The recent identification and isolation of the T-cell receptor and the cloning of the genes responsible for its synthesis are major accomplishments that provide the opportunity to clarify molecular mechanisms controlling the immune system.

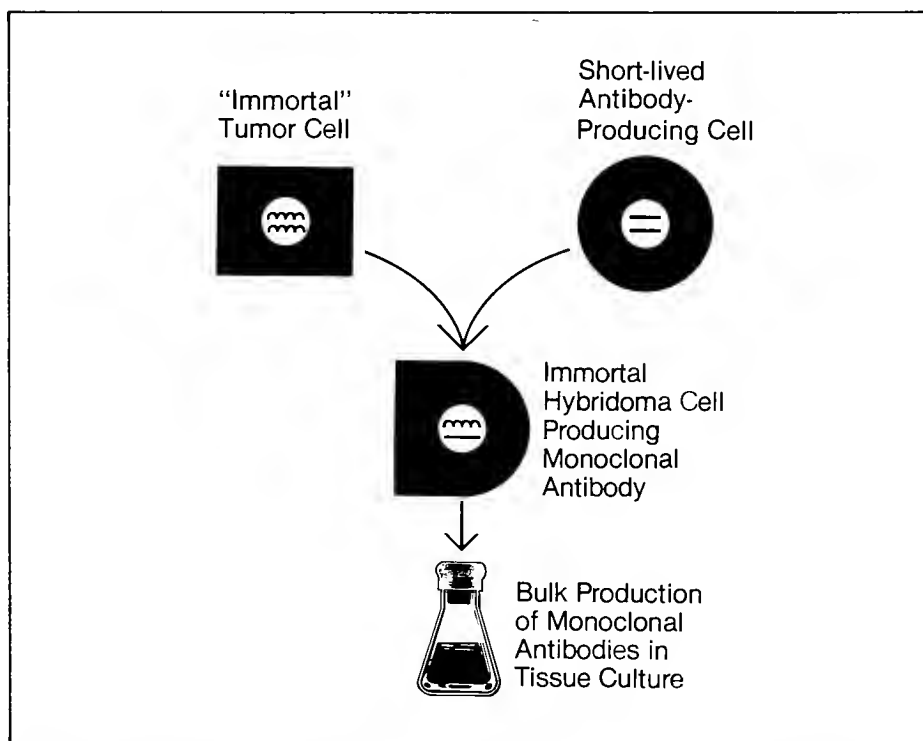
Research advances have been made by NIAID intramural scientists in understanding regulation of immune responses. A high molecular weight B-cell growth factor has been identified and purified. This factor promotes the growth of preactivated human B lymphocytes, the cells that produce antibodies. Inadequate control of B-cell growth factor production may be responsible for the pathogenesis of certain autoimmune diseases characterized by hyperactive B-cells. A monoclonal antibody directed against this factor has been developed, and cloning of the gene coding for the factor is in progress. Studies on the use of drugs to modulate B-cell function are showing some promise.

There are a number of diseases caused by a disorder of the immune system in which antibodies are produced that attack the patient's own tissues. Examples of these diseases are systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile diabetes mellitus, myasthenia gravis, and multiple sclerosis. Five-year survival rates of patients with SLE have improved from virtually zero in the 1950's to better than 90 percent today; this is due to earlier diagnosis as a result of more sensitive methods of detection, and improved methods of treatment. Specific "therapeutic" antibodies directed toward the autoantibodies have shown success in models of myasthenia gravis and multiple sclerosis, and preliminary clinical trials are under way.

Monoclonal antibodies are being employed in numerous ways in clinical and research laboratories. They are being used for rapid, precise diagnoses of infections and certain types of cancers, for clinical assays of enzymes and hormones, and for efficient purification of many substances. Many hybridoma cell lines, each producing a specific



*Autoimmune disease.*



*Cell fusion results in hybridoma, which produces monoclonal antibodies.*

monoclonal antibody, are being developed in scores of different laboratories. To ensure the availability of these valuable cell lines, contractual arrangements have been made between the NIAID and private institutions for the establishment of a repository and distribution center. In addition, maintenance of a hybridoma registry or "data bank" has been initiated so that detailed information about hybridomas can be stored in easily retrievable form.

Monoclonal antibodies have great potential in the treatment of human disease. Joining them to toxins may lead to the ability to selectively kill specific cells. This approach could prove useful in the treatment of severe infectious and autoimmune diseases, the reduction of immunologic rejection of organ transplants, and the elimination of tumors.

Research at the NIAID on regulation of immune function has benefited patients with certain vasculitides such as Wegener's granulomatosis, lymphomatoid granulomatosis, and polyarteritis nodosa. These diseases had significant morbidity and mortality before the introduction of medications studied at the NIAID which have resulted in cures in many patients. The mean survival of untreated Wegener's granulomatosis patients was 5 months, with 82 percent of patients dying within 1 year. Now 93 percent of patients treated according to a protocol developed at the NIAID, consisting of cyclophosphamide and prednisone, show complete remission.

The recent discovery of an interaction between the immune, endocrine, and nervous systems has potential importance in many clinical settings. As part of studies to understand these interactions, NIAID intramural scientists have demonstrated that two neuropeptides, adrenocorticotrophic hormone and beta endorphin, increased the proliferation of activated B-cells. Future studies will characterize the nature of the interaction of these

and other neuropeptides with cells of the immune system to help clarify the potentially very important interactions of immune-endocrine-neurologic networks.

### **Asthma, Allergies, and Inflammation**

Asthma and allergic diseases affect over 40 million Americans. Our knowledge of the causes and pathogenesis of these disorders is increasing rapidly, and it is evident that several areas offer exceptional opportunities for the development of improved methods of diagnosis, treatment, and prevention. Among the research areas, priorities include specific studies on allergic and inflammatory chemical mediators and pathways such as (1) the effect of Omega-3 fatty acids, which are present in fish-oil-enriched diets and have anti-inflammatory actions, in the prevention and treatment of asthma and allergic inflammatory disorders; (2) the role of naturally occurring neuropeptides in the production of asthma through their actions as neurotransmitting agents; (3) the design and development of new pharmaceutical agents to inhibit the cellular release of histamine, leukotrienes, platelet-activating factor and other chemical mediators of inflammation responsible for hypersensitivity reactions; (4) the chemistry of antigens that function as allergens; and (5) the pathophysiologic mechanisms of allergen-induced respiratory tract, gastrointestinal, and skin diseases resulting from mast cell discharge.

A key to ameliorating allergic reactions lies in the control of IgE antibodies. Recently, genes coding for IgE binding factors have been cloned. These IgE binding factors play important roles in the regulation of the synthesis of IgE. The cloning of these genes could lead to significant breakthroughs in the development of pharmacologic agents to prevent and/or control allergic diseases.

The effects of certain food additives, air pollutants, and commonly used pharmaceuticals in the production of severe asthma and life-threatening anaphylactic shock reactions are being reported with

increasing frequency. Certain volatile chemical agents prevalent in industry are also being increasingly recognized as causes of occupationally incurred asthma and immunologic lung diseases. An NIAID grantee has clarified how the industrial chemical, trimellitic anhydride, reacts with human airway proteins to produce trimellityl-protein complexes with new antigenic determinants; these complexes immunize the host and, on reexposure, result in immunologic diseases in the lung.

The NIAID is concerned with the widespread problem of adverse drug reactions, many of which can be life-threatening. Procainamide hydrochloride is the most commonly prescribed agent for treating abnormal heart rhythms. Within 1 year of treatment, approximately 50 percent of patients taking this agent develop autoimmune-type antibodies similar to those characteristically found in systemic lupus erythematosus (SLE). Such immune responses can be detected in virtually all patients maintained on long-term use of the drug. Of those who develop this autoimmune response, some 10 to 20 percent actually manifest clinical expressions of drug-induced SLE; of these as many as half will continue to have symptoms persisting even after drug withdrawal. In studies of this phenomenon, patients shown to exhibit slow natural inactivation of the drug by acetylation apparently develop autoimmune responses more rapidly than those capable of rapid elimination by fast acetylation. Another study has shown that antihistone antibodies are the predominant autoantibody in these patients, and that these antibodies can activate the classical complement pathway. Additionally, fruitful leads have been offered through indications of possible tissue-specific type (HLA) associations with the development of drug-induced SLE.

The NIAID has recently begun a 5-year multicenter study of the efficacy of injection treatments in adult asthmatics allergic to either ragweed or house dust mites. Also under way is investigation of the efficacy of injection treatment pro-



grams for those at risk of allergic reactions to animal products through occupational exposures or from household pets. Severe allergic reactions to fire ant stings are seen increasingly as a result of the migration of this insect in the United States. Studies are under way to identify active venom components and to develop materials for injection treatments of this condition.

Several lines of investigation are providing valuable leads for increased understanding of the many causes and triggering mechanisms in the production of asthma. While the association of infections with exacerbation of asthmatic episodes has long been recognized, new studies are providing valuable leads for defining a specific role for virus infections in asthma. Laboratory data suggest that influenza viruses may cause increased release of histamine from basophil cells and an alteration in other white blood cell (granular leukocyte) functions. Studies on parainfluenza viruses are indicating how they affect cell receptors responsible for bronchial muscle contractile responses to inflammatory substances, resulting in hyperreactivity of the airways.

The syndrome of exercise-induced anaphylaxis, described recently, is characterized by the onset of itching, warmth, generalized hives, gastrointestinal symptoms, collapse, and upper respiratory distress. As a result of research based on biochemical and electron microscopic studies of tissue sections, it has been demonstrated that exercise-induced anaphylaxis is a distinct form of physical allergy associated with activation of mast cell degranulation and resultant secretion of chemical mediators of inflammation.

NIAID intramural scientists are conducting studies on the interaction of chemical mediators of inflammation with certain white blood cells, called phagocytes, important in microbial killing. These studies include unraveling the mysteries of phagocyte-directed locomotion (chemotaxis), phagocytosis and generation of toxic products such as hydrogen peroxide, hypochlorite, and chlorine. Proper control of the release of these materials is essential

to a normal inflammatory response; too little inflammation leads to a compromised host and recurrent infection, while too much inflammation leads to inflammatory disease. Patients with defects of these host defense components have been studied intensively at NIAID. One group of patients has chronic granulomatous disease characterized by a lack of hydrogen peroxide generation by neutrophils and monocytes, and by recurrent life-threatening infections due to certain bacteria and fungi. Phagocytes from some of these patients have been shown to lack cytochrome b, a specific component of the enzyme system responsible for hydrogen peroxide generation. Studies are proceeding to define the missing or defective gene(s).

As part of an effort to understand the pathogenesis of inflammatory diseases resulting from unchecked inflammation, NIAID scientists have developed a simple quantitative enzyme-linked immunosorbent assay (ELISA) for complement products that are potent mediators of inflammation. The ELISA assay was used to measure the concentration of fluid phase complement complexes. The complexes were not detected, or only poorly detected, in patients with noninflammatory central nervous system diseases, but were readily detected in the spinal fluid of most patients with acute Guillain-Barre syndrome or multiple sclerosis, suggesting that terminal complement components participate in the tissue-damaging processes in these diseases.

Mast cells cause not only the classic signs of allergy (acute onset of sneezing, pruritis, erythema, whealing) but also initiate a prolonged inflammatory reaction. The reaction is due to "inflammatory factors" which attract certain white blood cells (neutrophils and eosinophils) to the site of allergic reactions. This response evolves over 4 to 8 hours and is the mechanism for chronic asthma following allergen exposure. It is this inflammatory response that causes the irritability of the asthmatic airway—which is the hallmark of asthma. It is the

chronic phase of the allergic response that responds to corticosteroid therapy. The use of corticosteroids in asthma may be designed to prevent or reverse airway inflammation and, as a consequence, airway irritability, with major effects on the prognosis and lifestyle of millions of Americans.

Many Americans believe they are "allergic" to one or more foods. This belief derives from food-related symptoms, often quite vague and nonreproducible. Skin testing patients with food idiosyncrasies reveals that even in the group with dramatic "anaphylaxis-like symptoms," only half had positive skin tests. Employing freeze-dried foods in opaque capsules, oral challenge in the skin-test-negative group was universally negative. Provocation of the skin-test-positive group revealed about 50 percent responding to double-blind, placebo-controlled challenges. Such data are useful for the proper evaluation and treatment of these patients.

### Organ Transplantation

Survival rates for all types of solid organ transplants have improved markedly. Currently, 75 percent of heart transplants, 70 percent of liver transplants and 75 to 80 percent of kidney transplants survive for 3 years. These favorable statistics have resulted from research in three areas: (1) immunosuppression of the rejection response, (2) enhancement of organ preservation techniques, and (3) improvements in donor-recipient matching.

The use of molecular biological methods has led to improved donor-recipient matching. The structures of the major human transplantation antigens (the tissue-specific histocompatibility complex) are being elucidated by a study of their genes and preparation of monoclonal antibodies to proteins prepared from cloned genes. The reagents developed through these techniques are being used to identify those cell surface molecules, present on donor organs, that must be matched in donors and recipients in order to prevent rejection.

Extensive clinical trials are in progress in which monoclonal antibodies are used to destroy cellular elements of the immune system responsible for rejection of kidney and bone marrow transplants. Because bone marrow transplantation is used to reconstitute the immune system when it has been compromised by hematological malignancy or inherited or acquired immunodeficiency, it is critical to prevent rejection of the transplant with minimal adverse effects.

The cells that cause organ transplant rejection do so both by direct cellular action and through the mediation of soluble secretions of certain lymphocytes known as lymphokines. Manipulation of lymphokine production is being investigated as a means to increase graft survival.

The use of cyclosporine has been a major contributor to transplantation success. Researchers are investigating the mechanism of cyclosporine action and its toxic effect on the kidney with the goal of developing analogs with increased effectiveness and decreased toxicity.

The effectiveness of organ preservation is a key factor in organ transplant success. Much injury to organs is caused by highly toxic metabolic products. This injury can be blocked by agents that prevent the generation, or interfere with the action, of these metabolites. Studies in animal models have confirmed the usefulness of these reagents and will be followed by evaluation in humans.

### **Acquired Immunodeficiency Syndrome (AIDS)**

The expertise of NIAID intramural staff and extramurally supported investigators, coupled with the momentum of ongoing research in the areas of virology, molecular biology, immunology, clinical infectious diseases, and immunoregulation, allowed a quick response to the public health emergency presented by the acquired immunodeficiency syndrome (AIDS). This syndrome is an infectious disease of the immune system that predisposes its victims to other opportunistic infections. It is a sexually transmitted

disease with important implications for the field of tropical medicine. All of these areas are of primary concern to the NIAID, and this Institute has accepted a major responsibility for research on this devastating disease.

Since the recognition of AIDS in 1981, the NIAID's Intramural Research Program has steadily increased basic and clinical research on this disease. NIAID investigators were responsible for the precise delineation of the immune defect that characterizes AIDS. To coordinate its extramural effort, the NIAID early in 1986 established the Acquired Immunodeficiency Syndrome Program at the organizational level of the previously existing Microbiology and Infectious Diseases Program and the Immunology, Allergic and Immunologic Diseases Program. The AIDS program is administering grants and contracts for (1) studies of the epidemiology and natural history of the disease, including a large study of 5,000 homosexual men; (2) the development and clinical testing of antiviral agents active against HTLV-III (the virus that causes AIDS), of agents and procedures for reconstitution of the immune system, and of agents for treatment of the opportunistic infections that kill individuals with AIDS; and (3) the development and clinical testing of candidate vaccines for prevention of HTLV-III infection.

HTLV-III has been studied extensively. Scientists have isolated the virus from individuals in several geographic locations, using molecular biologic techniques to characterize it and clone the genome. Comparison of isolates has revealed heterogeneity in the genome, largely within the viral envelope genes. Isolates from Central Africa were significantly different from a variety of North American isolates. Differences were seen also in biologic properties, especially in growth rates and ability to infect target tissues. These observations have significant implications for vaccine development.

Studies of the molecular structure of the virus have led to the development of an infectious clone, which currently is being propagated in a cell line. In addition, DNA probes have been made that have been used to detect virus in peripheral blood and bone marrow. A variety of DNA clones coding for different regions of the AIDS virus genome have been expressed in prokaryotic systems (i.e., bacterial cells such as *Escherichia coli*). The expressed proteins should provide excellent reagents for delineation of the precise nature of serologic and cellular immune responses to the virus. A variety of monoclonal antibodies against individual viral components have also been developed. These monoclonal antibodies may be of clinical relevance in that they may block the activity of the virus.

Animal models of AIDS are being developed. NIAID scientists were the first to transmit the infection to a nonhuman primate by inoculating chimpanzees with plasma from patients with lymphadenopathy syndrome. In a strain of mice infected with a murine leukemia retrovirus, a model for the lymphadenopathy syndrome seen in AIDS-related complex (ARC) has been developed. Further study of these models should assist the development of preventive and therapeutic approaches to AIDS.

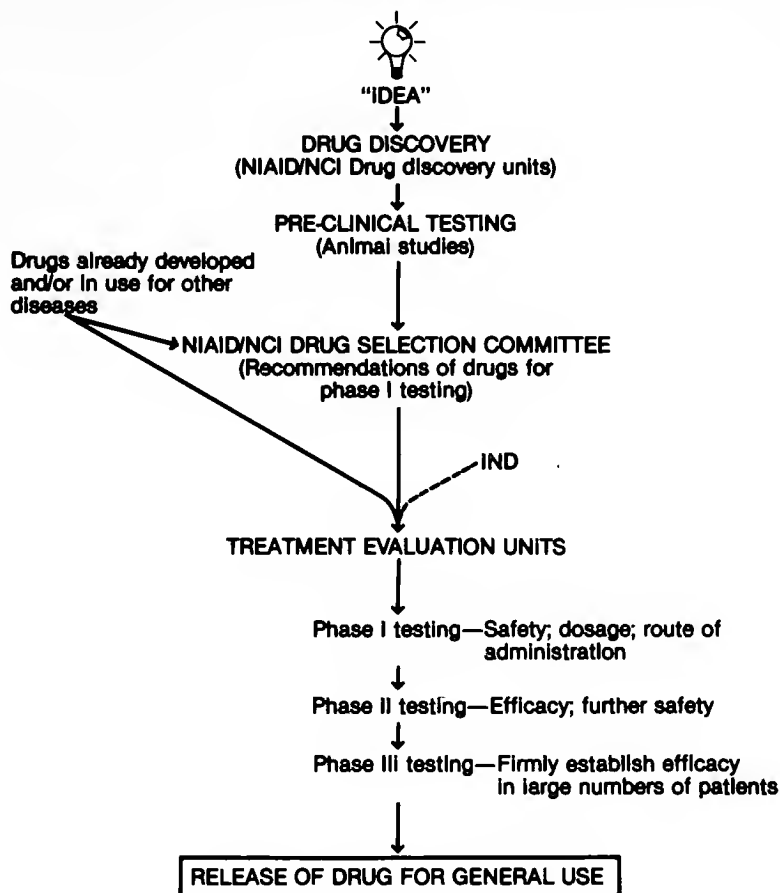
A defect in the ability of lymphocytes from AIDS patients to kill infected target cells *in vitro* has been corrected by interleukin-2 (IL-2). As a result, clinical studies to try to reconstitute the impaired host defenses in AIDS with IL-2 have been initiated. Gross and microscopic regression of Kaposi's sarcoma, one of the cancers observed in AIDS patients, has been seen following treatment with IL-2. In other studies, attempts at cellular reconstitution have been made by bone marrow transplantation and lymphocyte transfusion in identical twins. Partial transient correction of the impaired immune system was achieved by these techniques. Thus, it is possible to improve transiently the immune dysfunction in AIDS; but the data indicate that for this immune reconstitution to be of

clinical relevance, it will have to be done in connection with successful antiviral therapy against HTLV-III.

Cytomegalovirus (CMV) infection is a particularly severe problem in patients with AIDS. CMV remissions have been achieved in some patients, although a major problem remains in that the remissions are short-lived and chronic maintenance therapy is required. NIAID-supported contractors have synthesized and tested several compounds targeted for action against CMV. Several appear to interfere with the replication of CMV in host cells and are ready for testing in animal models.

The NIAID, in collaboration with the National Cancer Institute (NCI), has developed a comprehensive program for the development and clinical evaluation of agents and procedures for treatment of AIDS, ARC, and opportunistic infections. The program involves joint NCI-NIAID grant-supported National Cooperative Drug Discovery Groups, which will use modern technology to discover new candidate anti-HTLV-III drugs, and the establishment of NIAID contract-supported screening units to evaluate candidate drugs for *in vitro* anti-HTLV-III activity. Preclinical testing in animals is being performed by the NCI. Evaluation of drugs for further testing in clinical trials is being done by the joint NCI-NIAID Drug Selection Committee that has non-Government expert representation. Phase I and phase II clinical testing will be carried out in a number of AIDS Treatment Evaluation Units to be established throughout the country, supported by NIAID contracts. These units will evaluate candidate agents against HTLV-III, agents and procedures for immune reconstruction, and agents for treatment of opportunistic infections. Future efficacy trials will be done either through a network of these units or through new contracts for multicenter efficacy trials. These units will allow evaluation of treatment regimens to proceed much more quickly than is now possible and will allow a much larger number of AIDS and ARC patients access to well-designed and well-managed treatment studies.

## STEPS IN DEVELOPMENT AND TESTING OF THERAPEUTIC AGENTS AGAINST AIDS RETROVIRUS



Steps in development and testing of therapeutic agents against AIDS retrovirus.

A major emphasis by NIAID intramural scientists has been on the development of vaccines to prevent AIDS. An envelope gene of HTLV-III has been expressed in a vaccinia virus vector; sera from AIDS patients reacted with the recombinant protein. In addition, mice immunized with the recombinant virus produced antibodies that reacted with the envelope protein of HTLV-III. Efforts to determine if the recombinant vaccinia virus will prevent HTLV-III infection in animals are in progress.

While NIAID vaccine development efforts are still in the laboratory phase, the NCI is currently evaluating for safety and antigenicity in animals, candidate vaccines made

by extracting antigens from whole virus. When candidate vaccines are ready for human studies, phase I clinical evaluation for safety and immunogenicity will be performed in existing NIAID-supported vaccine evaluation units. Additional vaccine evaluation units and efficacy trials will be added in future years as needed.

Opportunistic infections in patients with AIDS are receiving increasing attention. Recent studies indicate that gamma interferon appears to be the key T-cell produced lymphokine responsible for activating human monocyte-derived macrophages to kill intracellular pathogens. AIDS patients with bacterial infections caused by *Mycobacterium avium-intracellulare*

typically have heavily infected tissues at autopsy despite conventional antibacterial therapy. It has been demonstrated that the T-cell defect of these patients extends to absent or markedly impaired T-cell proliferative and gamma-interferon-generating activity in response to stimulation with specific bacterial antigens. Through a number of NIAID contract-supported extramural projects, investigators are attempting to develop improved treatments for a number of opportunistic infectious agents including *Mycobacterium avium-intracellulare*, *Pneumocystis carinii*, *Candida albicans*, and cytomegalovirus.

#### **Program Policies**

In FY 1985, the NIH placed the highest priority on the funding of investigator-initiated research project grants (RPGs). The NIAID placed an even greater priority on RPGs and will continue with this policy.

The NIH began 99 years ago as an intramural laboratory, doing infectious disease research. Over the years, the NIH has grown to include more than infectious disease research, and to allocate most of its funds extramurally rather than intramurally. However, the NIAID has continued to support a major, highly productive, intramural research program, not only in infectious diseases, but also in immunology. The commitment to a vigorous intramural research program, doing both basic and clinical research, located in Bethesda and Frederick, Maryland, and Hamilton, Montana, will continue.

In FY 1985 research centers constituted only 2 percent of the NIAID budget. The 18 NIAID centers are either Asthma and Allergic Disease Centers (AADCs) or Centers for Interdisciplinary Research on Immunologic Diseases/CIRIDs). Their objective is to accelerate the clinical application of new knowledge of the immune system. A special feature of these centers is dissemination of information to physicians and patients through special projects and activities.

In collaboration with the CIRIDs and other groups, the NIAID has sponsored a series of outreach/technology transfer conferences for primary care physicians and health care workers on AIDS, immune system disorders, childhood immunodeficiencies, organ transplantation and systemic lupus erythematosus at sites around the country. Over 17,000 individuals have participated in these NIAID-organized conferences.

During FY 1985 the NIAID made the first award under its new Minority Research Enhancement Program. The Institute has also continued awards to Historically Black Institutions, support of the Minority Biomedical Support and Minority Access to Research Career Programs, and an annual Introduction to Biomedical Research Program for minority students.

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## **The Biennial Report of the Director, National Institute of General Medical Sciences**

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### **History**

The following events represent milestones in the development of the National Institute of General Medical Sciences (NIGMS).

- July 16, 1958—The Secretary of DHEW approved the establishment of the Division of General Medical Sciences.
- October 17, 1962—Public Law 87-838 authorized establishment of an Institute to conduct and support research and research training in the general or basic medical sciences and in related natural or behavioral sciences that have significance for two or more other Institutes of NIH, or that lie outside the general areas of responsibility of any other Institute.
- January 30, 1963—The Secretary of DHEW approved the establishment of NIGMS.
- December 2, 1963—The National Advisory General Medical Sciences Council met for the first time.
- September 1, 1974—Dr. Ruth L. Kirschstein was appointed Institute Director.

### **Introduction**

The National Institute of General Medical Sciences supports research and research training in the basic biomedical sciences that form the foundation needed to make advances in the understanding of disease. In this way, the Institute helps supply new knowledge, theories, and concepts for the disease-targeted studies supported by other NIH components. NIGMS' research training programs help provide the most critical element of good research: well-prepared scientists.

The Institute now has five major program areas. Four of these—Cellular and Molecular Basis of Disease (CMBD), Genetics, Biophysics and Physiological Sciences (BPS), and Pharmacological Sciences—award grants for research

projects and research training. The fifth program, Minority Access to Research Careers (MARC), aims to increase the number and capabilities of minority individuals engaged in biomedical research and teaching by awarding research training grants and fellowships.

NIGMS is a major source of NIH research training support, funding two-thirds of the predoctoral trainees and about one-third of all the trainees who receive assistance from NIH. In its research training programs, as in its research interest areas, NIGMS stresses the importance of laying the basic groundwork for disease-oriented research as well as for further fundamental biomedical studies.

Interprogram coordination is also emphasized, since projects and developments in one area frequently are relevant and of consequence to others. The Institute fosters multidisciplinary approaches to research and employs a full range of support mechanisms.

The Institute has no laboratories on the NIH campus, although it does sponsor a small program in which research fellows work in the laboratories of other NIH Institutes in areas related to the pharmacological sciences. All of the other activities NIGMS supports take place at universities, medical schools, hospitals, and research institutions throughout the country and abroad.

It is often difficult at the beginning of a research project in the basic sciences to predict where it will lead. Indeed, if it is worthwhile research, the outcome must be uncertain. Yet it is this kind of basic research from which so many of the great advances in the biomedical sciences come—the kind of advances that revolutionize our way of looking at life processes, and that yield results—and may save on health care costs—in the form of improved treatment, prevention, or cures of many different diseases.

While the word “basic” may have connotations of simplicity, these connotations do not apply to basic biomedical research such as that supported by NIGMS. In this context, “basic” signifies the fundamental nature of studies in such

areas as the structure and function of cell components, genetic principles, and mechanisms of drug action. Going back as far as the 1950's, for example, basic investigations in cell biology and immunology provided today's scientists with the tools to grow the AIDS virus in cell culture. Fundamental studies of gene structure and function made possible the discovery and elucidation of oncogenes (genes involved in the development of cancer). The basic research being conducted today will be at the root of similar advances in the future.

An additional way in which basic research contributes to all science is in its development of new techniques and tools that facilitate further studies. Recombinant DNA technology—amazingly only 13 years old, despite its enormous impact on research, medical care, industry, and agriculture—is one example. Another example is the instruments, such as sophisticated microscopes and powerful computers, that have made it possible for biophysicists (scientists who apply the principles of physics to the study of biological phenomena) to examine detailed molecular structures. For instance, a team that has received over 20 years of NIGMS support for structural studies of proteins and other molecules recently became the first group to map the detailed structure of an animal virus—in this case, a human cold virus. The knowledge gained through this research may someday enable scientists to find ways to fight the common cold. Moreover, the technology developed in the course of this work can now be applied to study the atomic structure of a variety of other molecules.

NIGMS has also played an important role in supporting the studies that underlie many of the biotechnological advances that are beginning to make significant contributions to both human health and the Nation's economy, as well as dramatically changing biomedical research itself. Biotechnology today is enabling scientists to observe and manipulate the genetic makeup of living organisms, creating previously unimaginable opportunities to unlock the

secrets of biology. This capability is the result of research investments made 10, even 20, years ago, largely by NIGMS.

Over the years, NIGMS has supported the work of a substantial number of Nobel Prize winners and other award-winning scientists. The past 2 years were no exception. The recipients of the 1985 Nobel prize in Physiology or Medicine and a 1985 Lasker Award, Dr. Joseph L. Goldstein and Dr. Michael S. Brown of the University of Texas Health Science Center at Dallas, were investigators on two NIGMS grants from 1972 to 1977. During this period, they made the fundamental discovery of the receptor involved in cholesterol metabolism, work that was called “a milestone” by the Nobel Committee in its announcement of that prize.

NIGMS also provided support to Dr. Herbert A. Hauptman of the Medical Foundation of Buffalo, who shared the 1985 Nobel Prize in Chemistry with Dr. Jerome Karle of the U.S. Naval Research Laboratory. These scientists were honored for developing mathematical techniques to determine the three-dimensional structures of small molecules in a much more rapid and direct way than was previously possible.

Knowledge of the detailed structure of molecules has important implications for the development of new drugs as well as for understanding how biological substances, such as hormones, function in the body. The approach taken by Drs. Hauptman and Karle greatly improves the information that can be obtained from x-ray crystallography, a technique that provides structural data about molecules by passing x-rays through crystals of the molecules and recording on film how the molecules scatter light. The analysis of these patterns of diffraction was extremely difficult, time-consuming, and often inexact until Drs. Hauptman and Karle devised formulas for comparing the relative intensities of the spots of film darkened by the x-rays. With the aid of powerful computers, analysis can now be done in a matter of days, rather than taking years, as it did in the past.

Another award winner recently supported by NIGMS is Dr. Paul Lauterbur of the State University of New York at Stony Brook, recipient of both a 1984 Lasker Award and a 1985 General Motors Award for his work in refining nuclear magnetic resonance (NMR) instrumentation for use in diagnostic imaging. Dr. Robert Schimke of Stanford University, an NIGMS grantee for the past 20 years, was also a 1985 General Motors Award winner. He was honored for his research showing that cancer cells can develop resistance to a tumor-killing drug, methotrexate (MTX), through a spontaneous process in which the treated cells make extra copies of the gene that codes for the enzyme dihydrofolate reductase. This is the same enzyme upon which MTX acts to bring about the cell's death.

Finally, five individuals who received NIGMS support for their research endeavors have recently been given the prestigious National Medal of Science by the President. Among the 1985 awardees were Dr. Paul Berg and Dr. Richard Zare, both of Stanford University, and Dr. Roald Hoffmann of Cornell University. Drs. Berg and Hoffmann are also Nobel Prize winners. In 1986, National Medals of Science went to long-time NIGMS grantees Dr. George Palade and Dr. Joan Steitz, both of Yale University.

## Research Programs

### Cellular and Molecular Basis of Disease

The Cellular and Molecular Basis of Disease Program supports a broad range of research at the most fundamental levels of biology, involving the cell and the molecules that make up the cell and its environment. The purpose of this work is to gain a better understanding of life processes that could eventually lead to ways to fight diseases that result from disturbed or abnormal cellular activity.

Cell biology as we know it today is a relatively young discipline. In the past few decades, greatly improved microscopes and other sophisticated new techniques, such as better methods for separating and

analyzing cell components, have revealed an amazingly complex, highly structured world within the cell. It is a world of constant motion where thousands of chemical reactions occur each second. Each cell has its own power plant, digestive system, factories for making proteins, and an intricate communications network that regulates activities, sends and receives signals, and senses changes in the environment. The proper functioning of all parts of a cell, from its outer membrane to the tiny internal structures known as organelles, is crucial to the health of the whole organism.

All cells, from those of one-celled plants or animals to those of complex creatures like human beings, contain the same fundamental materials. This is one reason researchers in the basic biomedical sciences can make use of model organisms like bacteria or fruit flies for their studies. In addition, the great variety in cell size, shape, and function—even within the same organism—allows scientists to select cells with special characteristics that make the problems to be studied simpler or more obvious. Regardless of the model system used, the researcher's goal is always to gain a greater understanding of processes that occur in or affect humans.

One area of tremendous excitement is research on cell membranes. Each cell is surrounded by a membrane that controls the movement of substances into and out of the cell. In addition, intracellular membranes form organelles such as the nucleus and the mitochondria. Membranes play a central role in cell physiology, particularly in growth control and hormone action. Among the processes scientists are looking at are the mechanisms by which proteins reach their proper membrane location, the biochemical pathways by which membrane constituents are recycled, and the chemistry of the receptors that control the transport of specific molecules across cell membranes.

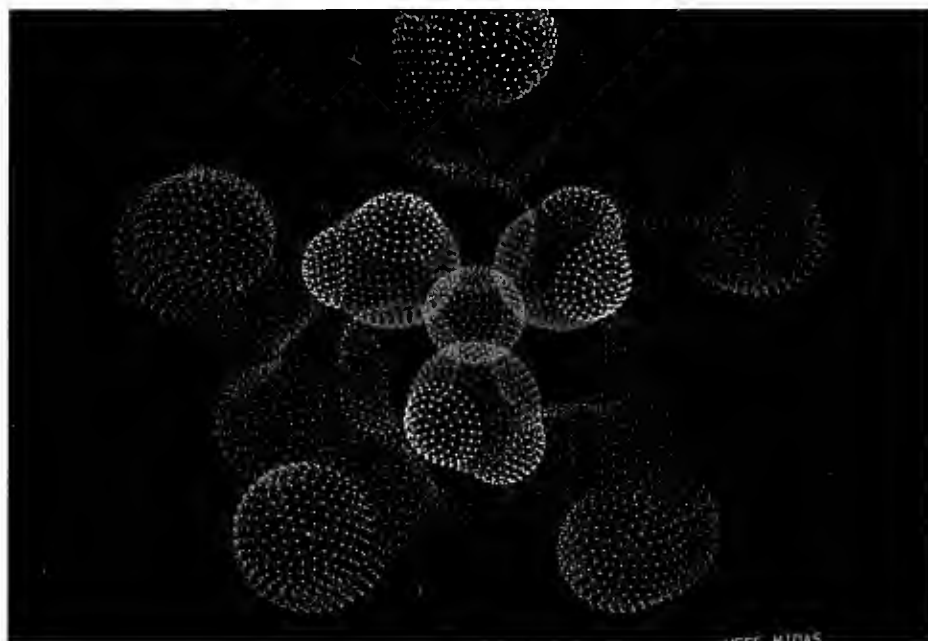
Receptors themselves are the focus of a good deal of research supported by this program. Some receptors, such as the one for cholesterol

discovered by Nobel Laureates Drs. Brown and Goldstein, recognize and internalize specific molecules that cells need. For example, scientists are studying how the receptors in the membranes of the cells lining the intestines recognize and then transport the amino acids (protein building blocks) critical to the digestive process. Other grantees are examining receptors that perform a second important function, that of receiving and transmitting the protein "signal" molecules that influence or control cell activity. This class of receptors includes the one for epidermal growth factor, or EGF, a protein that appears to play a role in controlling cell division. Interest in EGF is intensifying because of evidence that its gene may be similar to an oncogene. Thus, studies of EGF receptors may have far-reaching implications, not only for understanding normal cells but also for explaining how they become malignant.

Another area that holds great promise is studies of the cellular aspects of immunology. New knowledge in immunology could help scientists understand a variety of diseases, including cancer, AIDS, arthritis, and diabetes. In addition, cells of the immune system provide excellent models for addressing basic questions in cellular and molecular biology, such as the complex interactions between cells and the mechanisms of cell activation and differentiation into specialized tissues, like skin or muscle.

A number of NIGMS grantees are investigating aspects of direct cell-to-cell communication (known as cell coupling), which is found in virtually all animal tissues from the simplest invertebrates to mammals. The most obvious function of cell coupling is that of electrically coordinating certain cell communities for synchronous activities, such as heart contraction to pump blood and uterine contraction during labor. In addition, cell coupling appears to play a special role in development. These researchers are learning a tremendous amount about the structure and function of the channels that connect cells. This knowledge should in turn lead to a better





Computer-generated, cross-sectional model of the ion channel in the receptor for the neurotransmitter acetylcholine.

understanding of the role of inter-cellular communication in many life processes.

Other scientists supported by the CMBD Program are studying enzymes, the highly efficient catalysts of the chemical reactions that are essential to the functioning of living cells. These catalysts are proteins that possess a particular site that recognizes a target molecule, binds it, and changes it in some way; typically, enzymes possess one such site and thus have one catalytic function. However, it is becoming clear that some enzymes possess a number of different catalytic sites. These substances, known as multifunctional enzymes, carry out all, or at least many, of the reactions in a given metabolic pathway. For example, one investigator has determined that fatty acid synthetase is a multifunctional enzyme that effects a seven-step series of reactions yielding the fatty acid palmitate, a structural component of cell membranes. The importance of multifunctional enzymes is generally thought to reside in the enhanced metabolic activity they provide. It is also believed that incorporating numerous enzymatic functions into one protein allows the cell to regulate a number of enzyme activities (or even an entire meta-

bolic pathway) coordinately. Investigators are examining multifunctional enzymes in an effort to answer certain fundamental questions, including the relationship between an enzyme's structure and its multiple functional sites, whether the functional sites are always independent, and the exact nature of the reactions facilitated by these enzymes.

Calcium, an element that is essential for the normal functioning of living cells, is the subject of much research funded by the CMBD Program. Processes such as blood clotting and muscle contraction are dependent on the presence of calcium. Moreover, numerous enzymes and hormones require calcium in order to be biologically active. Scientists are making new discoveries about the mechanism of calcium action and the role it plays in regulating cellular processes. Their findings will shed light on this important aspect of cell biology and may have implications for the treatment of disorders involving defects in calcium function at the cellular level.

Researchers working with NIGMS funds are also investigating respiration, the processing of energy-rich "fuel" molecules to provide cellular

energy. This is an extremely complex event in higher organisms that has proved difficult to study. Now, however, one scientist has found a simple respiratory system in the membrane surrounding the bacterium *Paracoccus denitrificans*. This system appears to be functionally identical to that of mitochondria, the organelles responsible for respiration in eukaryotic cells (the cells of a large class of organisms that includes mammals). The system, which is now being perfected, should become an excellent model in which to study the molecular basis of the vital process of respiration in higher organisms.

### Genetics

The NIGMS Genetics Program focuses on research that will yield a better understanding of basic genetic processes and the mechanisms of inheritance in health and disease. Over 120 years ago, scientists began to deduce the existence of genes as discrete units of heredity responsible for specific traits and to study patterns of inheritance. Today, advances in biomedical research are enabling us to learn how genes and their products act biochemically. This knowledge is greatly improving our ability to understand genetic processes and the more than 3,000 genetic disorders.

The role of genetics in human disease can be seen most clearly in the so-called "single-gene" disorders, which range from relatively minor conditions like color blindness to devastating illnesses such as Tay-Sachs disease or sickle-cell anemia. Now, scientists are seeing evidence that many common diseases like diabetes, hypertension, atherosclerosis, and cancer involve genetic changes or a genetic predisposition to the illness as well as environmental factors. Thus, a fundamental understanding of genetics should contribute to improved treatment of a variety of disorders, as well as reduce the staggering health care costs associated with these conditions.

Knowledge in the field of genetics is growing rapidly. It was just 33 years ago that deoxyribonucleic acid (DNA) was proved to be the basic hereditary material. Genes were then shown to be segments of DNA

carried on chromosomes, to contain the information for all inherited characteristics, and to code for the synthesis of proteins. Today, scientists can insert new genes into bacterial, plant, and animal cells in test tubes to study the mechanisms of genetic control as well as to direct the cells to make substances important to humans. More sophisticated basic research is made possible by a variety of new technologies that allow the isolation and examination of large DNA fragments, the rapid determination of the sequence of DNA subunits, and computer-assisted identification and comparison of the sequences of genetic material.

One important research area in which the new technology is beginning to provide answers to many difficult questions is that of developmental genetics. Molecular biology is at a stage where we can examine the basic control mechanisms behind cellular differentiation—the process that is the basis of all multicellular life.

Over the years, a great deal has been learned about the genetics of fruit flies. These organisms are ideal for genetics research because of the ease with which their genetic material can be studied and their short life cycle, which permits the effects of genetic changes to be determined relatively quickly. Now this body of knowledge is providing a rich foundation for complex studies of how the information contained in the genetic code is translated into three-dimensional structures in the organism. The results of such research are expected to have a bearing on our understanding of normal development and how it malfunctions in a wide range of species, including humans.

As sometimes happens in the study of fundamental biological processes, an NIGMS grantee has discovered an exception to a principle that was previously assumed to apply to every living creature on earth. This investigator is one of a number of scientists who found that the genetic code—the system by which information held in DNA and the related genetic material, RNA, is translated into protein products—is



*Male fruit fly (Drosophila melanogaster), a common model for genetics research.*

slightly different in a type of single-celled organism called a ciliated protozoan. A particular sequence of genetic information that in most organisms signals "stop making protein" instead specifies the insertion of the amino acid glutamine into the protein chain in this protozoan. Prior to this finding, scientists thought that the genetic code was universal; that is, a given sequence held the same information regardless of the organism in which it existed. In fact, the majority of organisms do share a common genetic code—this is what makes recombinant DNA research so successful. But the finding of an exception raises many questions that can only be answered by further studies in this area, which may provide new clues about the evolution of the genetic code.

Progress has also been made in the development of methods for pinpointing the chromosomal locations of genes, a process known as gene mapping. This effort involves many dedicated teams of researchers throughout the country, a number of whom receive Genetics Program support. At last count, over 400 human genes had been definitively mapped, with another 400 tentatively

mapped. Abnormalities of almost 200 of these genes are known to cause human disease. Gene mapping represents a key step toward the development of better methods for diagnosing and treating these diseases, and will continue to be a high-priority activity supported by the Genetics Program in the future.

It is relatively easy to locate a gene whose protein product is known. Unfortunately, the primary protein defect has not been identified in many major disorders, such as cystic fibrosis, making it virtually impossible until recently to search for the gene or genes responsible for these diseases. The breakthrough came several years ago when researchers found that strands of DNA have patterns that vary between individuals. The more closely related people are, the more similar their DNA patterns will be. By comparing specific segments of DNA among a large number of people, some of whom have the disease for which the gene is sought, scientists can determine patterns that correspond to the presence of the defective gene. This approach has led to the discovery of stretches of genetic material associated with the genes responsible for Huntington's disease and cystic fibrosis. These so-called "markers" may form the basis of

diagnostic screening tests to determine either the absence of a particular gene or the presence of an abnormal gene.

Once markers for disease-causing genes are found and the location of these genes is pinpointed to a particular chromosome (and often, to a specific area of the chromosome), scientists can search for these genes more efficiently. This searching is aided by a technique whose development began in the late 1970's, spearheaded by an NIGMS grantee. The technique allows researchers to systematically work their way along a chromosome to locate and isolate a specific gene whose protein product is not yet known, and has already enabled scientists to discover a class of genes involved in development.

Significant advances have been made on other important fronts as well, with researchers learning more and more, for example, about the molecular machinery that works to turn genes on and off at just the right moments, and about the nature of the consequences when such machinery goes awry. Scientists are hopeful that they can eventually use the information obtained from such studies to gain an understanding of how the functioning of all genes is regulated. It is believed that this, in turn, will facilitate efforts to control some of the effects of genetic disorders.

At the other end of the basic research spectrum, some Genetics Program grantees are working on studies that eventually may make direct gene therapy possible as a cure for genetic disorders. The long-term goal is to be able to replace a defective gene with a normal one in some or all of the body's cells. Such treatment would affect only the patient, not his or her offspring, and would in some ways resemble an organ transplant. It is currently very difficult, however, to insert a normal gene into the correct site on a chromosome and have it be expressed in the proper amount at the proper time. If the gene is inserted inappropriately, it can disrupt normal genes or regulatory regions and could result in health problems as serious as the original disorder.

In many laboratories, great strides are being made toward the goal of effective gene therapy. Recently, two NIGMS grantees successfully inserted a gene into a predetermined site on a human chromosome. Working with cells grown in test tubes, these researchers managed to insert the gene for beta-globin, a component of hemoglobin, the oxygen-carrying protein of red blood cells. This gene is defective in blacks who have sickle-cell anemia, as well as in some persons of Mediterranean ancestry who have a different type of anemia called thalassemia.

The new work by these scientists is still in its early stages and cannot yet be applied to treat diseases. Nevertheless, it is very encouraging, because until now no one had been able to make planned modifications, such as targeted insertions, of specific genes of any organism more complicated than yeast. Their success raises the hope that modification of the defective beta-globin gene will be feasible as a treatment of—and perhaps ultimately a cure for—patients with genetic disorders such as thalassemia and sickle-cell anemia.

Finally, scientists supported by the Genetics Program have shed new light on the biochemical basis of the serious, potentially life-threatening wasting condition caused by certain infections, injuries, and cancers. They have found that the protein cachectin, which is produced in response to severe physiological stress, causes fat cells to release energy and prevents them from storing fat from food sources. While the initial burst of energy stimulated by cachectin has obvious value in fighting infections or injuries, the inability to maintain fat supplies can be debilitating and dangerous. Improved understanding of these mechanisms should help scientists devise means for preventing chronic wasting, and may also have implications for treating obesity. Interestingly, other researchers (one of whom is an NIGMS grantee) have found that cachectin is identical to a substance called tumor necrosis factor, a protein now being tested for its anticancer properties.

## Genetics Resources

To facilitate basic research on genetics and genetic diseases, NIGMS supports several resources that are available for use by Institute grantees and other interested scientists. These resources include the Human Genetic Mutant Cell Repository and the Genetic Sequence Data Bank (known as GenBank®). The cell repository, located at the Coriell Institute for Medical Research in Camden, New Jersey, was established in 1972 to help scientists study the role of mutations and other genetic errors in disease by giving them easy access to living cells that contain these changes. The repository houses nearly 3,600 cell lines representing more than 300 genetic diseases. Its collection includes cell lines with many types of chromosomal abnormalities; cell lines having identified biochemical defects, such as those from people with phenylketonuria; and cell lines in which the biochemical defect is still a mystery, as in Huntington's disease. In addition to cells from people with various hereditary diseases, there are cells from healthy carriers of these diseases and cells from normal volunteers available for comparative studies. A special feature of the repository is its collections of cells from large families with various diseases, as well as from normal families. These cells are of great value in detecting markers for diseases and for ultimately isolating the disease genes themselves. All cell cultures in the repository are available at modest cost to anyone doing research on genetic diseases, thus permitting the researchers to study aspects of many rare disorders without first having to locate a cell donor.

In contrast to the cell repository, there are no cell cultures and not even a piece of DNA or RNA in storage at GenBank—just computers and lists of genetic sequences from organisms as varied as bacteria, yeast, mice, and humans. Now that stretches of DNA and RNA of various kinds are being sequenced by researchers all over the world with increasing speed, a central library of sequences has become essential to prevent duplication of

effort and to enable scientists to compare what they have found with all other known sequences. Without GenBank, it would be impossible for researchers to do their own work and keep up with the flow of information in this field.

GenBank is an international repository of genetic sequences that are cataloged, checked for accuracy, and annotated for sites of biological interest. By the end of 1985, just 3 years after its inception, GenBank contained more than 6,000 entries representing some 5.6 million nucleotides (building blocks of DNA or RNA). Users can "call up" on their own computers or request a printout of any sequence in which they are interested and learn about many of its significant features—for example, which regions code for proteins. The data base allows researchers to search for similarities between a newly determined sequence and all existing sequences, and to do sophisticated analyses that might reveal other important regions.

### Biophysics and Physiological Sciences

The Biophysics and Physiological Sciences Program is a relatively new NIGMS component organized to emphasize research that uses the theories and tools of physics to study biological processes and the structures and properties of biological substances. The physiological sciences section of BPS includes a trauma and burn research program that supports studies on topics ranging from biological responses to injury to the development of artificial skin for burn victims. The program also supports research that applies engineering principles to the solution of significant biomedical problems, as well as the creation of new instruments and methods to facilitate research on such problems.

One of the most important areas of investigation in the field of biophysics is the development of approaches for determining the structure of complex molecules, since to a large extent a molecule's chemical properties depend on its structure. Because scientists cannot "read" amino acid or nucleotide se-

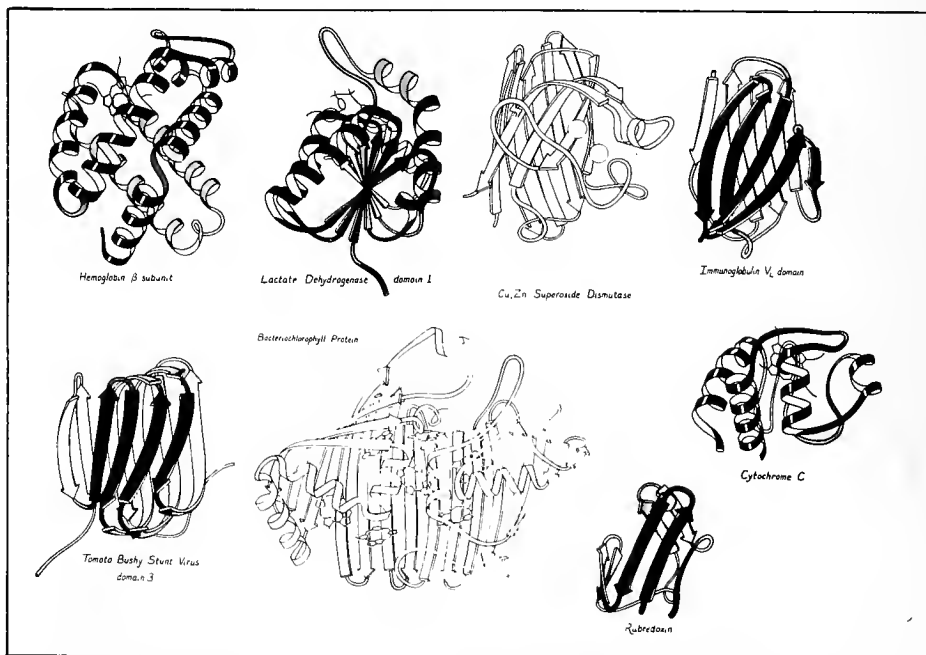
quences in such a way as to predict the detailed three-dimensional structure of large molecules, a variety of special techniques are used to arrive at this information.

For substances that form suitable crystals, x-ray crystallography is a valuable technique for determining structural details. Scientists employ this tool to examine the structure and function of proteins, enzyme complexes, and other important molecular systems. NIGMS grantees working in this area have used data from x-ray crystallographic studies to describe the atomic details of the bending of DNA. By one estimate, if all the DNA in a person's cells were uncoiled, it would stretch to the sun and back 50 times. How the DNA molecule bends and folds tightly enough to fit into the nucleus of a cell and yet becomes relaxed enough to allow genes to be copied as part of protein synthesis is an important question for structural biologists. Knowledge about DNA bending now being sought by NIGMS grantees may provide a key to understanding gene action, drug binding to DNA, and other fundamental processes.

Nuclear magnetic resonance spectroscopy is one of the most powerful noninvasive techniques being used by BPS grantees to determine the properties of molecules. This tool identifies substances by the way they absorb energy in magnetic fields. Researchers can use NMR to study substances in their natural state (as opposed to an artificially created, crystalline state) to gain insight into the complex regulatory functions of a host of biological systems. It also allows them to study the effects of changes in physiological conditions on metabolism in specific tissues and organs and on the transport of molecules across cell membranes.

NMR is making possible more detailed research on DNA, RNA, and proteins, including enzymes. Furthermore, after years as a basic research tool, this technique is now becoming a valuable aid for clinicians. Its use for imaging the human body is leading to significant improvements in the diagnosis of cancer, stroke, heart disease, multiple sclerosis, and other disorders.

Sometimes investigators create new scientific instruments or improve existing ones as a



*Schematic diagrams of protein structures obtained through x-ray crystallography. (Courtesy of Dr. David Richardson and Jane Richardson.)*

byproduct of their primary research. If there is no tool to do what they need, they simply develop one—and often other basic researchers, sometimes in different fields, also benefit. For example, an NIGMS grantee needed a way to analyze large segments of DNA for his genetics research. The standard method for such analysis, called gel electrophoresis, could only give good resolution on segments of up to about 70 kilobase pairs in length. (A base is one of the informational subunits of a DNA molecule; a kilobase equals 1,000 bases.) Yet the smallest known eukaryotic chromosomes—those of yeast or small blood cell parasites such as trypanosomes—are approximately 2,000 kilobase pairs long. To study these chromosomes, researchers had to break them into fragments and later reconstruct them to get a picture of an intact chromosome. The new method is a variation on gel electrophoresis that extends resolution to the 2,000 kilobase range. This investigator and his colleagues have already used the system to study trypanosomes, one species of which causes sleeping sickness, and they have found important new information on the mechanism by which the trypanosomes evade the body's immune system. It is conceivable that this technique might eventually allow scientists to study intact chromosomes of higher organisms such as fruit flies, mice, and even humans.

Another BPS grantee has used basic studies of the scattering of light to develop a technique that has the potential for identifying disease-causing microorganisms much more rapidly than is now possible. This system is based on the interaction of a microorganism's genetic material with polarized light beamed from different directions. Since the organisms do not have to be isolated and cultured prior to testing, identification can be made in minutes rather than hours or days. The shortened time it will take to reach a diagnosis using this technique should prove valuable in the treatment of many diseases, including spinal meningitis, septicemia,

pneumonic plague, and Legionnaire's disease, illnesses for which prompt diagnosis is particularly important for effective therapy. The investigator is planning improvements in the system to enable it to identify and estimate the relative quantities of microorganisms in samples that contain many different types of organisms, as do most clinical specimens. The device is expected to be marketed for clinical use by a private firm within the next few years.

Grantees of the BPS Program are also involved in applying engineering principles to the solution of significant biomedical problems. One promising area is the study of biomaterials used for artificial joints and how such implants interact with living tissue and body fluids. Other groups of biomedical engineers supported by NIGMS have designed implantable pumps and similar systems that can infuse drugs such as insulin into the bloodstream at a constant rate. These systems seek to avoid the peaks and falls in drug levels in the body that are characteristic of the administration of pills or injections.

The BPS Program's support of research on burns and other forms of trauma has the ultimate goal of saving some of the more than 100,000 lives lost each year to accidental injury, including burns. Studies are directed largely at gaining a better understanding of the profound body responses that follow severe injury. At special research centers supported by NIGMS, basic scientists working in such fields as biochemistry, physiology, and immunology collaborate with medical specialists who provide trauma and burn care. They work together so research advances can be applied quickly to the treatment of patients.

Areas studied by trauma and burn researchers include lung damage from smoke inhalation, skin replacement and wound healing, the massive metabolic upheavals caused by burns and other forms of trauma, and immune system alterations that can lead to life-threatening infec-



*An NIGMS-supported scientist holds a sample of artificial skin for burn patients.*

tions. The investigations focus on the basic physiological mechanisms that underlie each problem.

NIGMS-supported scientists have developed, and are now refining, a covering that serves as an artificial skin for severely burned patients. This material may someday reduce or eliminate the need for human skin grafts. Other researchers have discovered a protein that stimulates the growth of small blood vessels, a finding that may point to ways of speeding wound repair. A spinoff of this research, the preparation of an antibody to this protein, may help decrease blood supply to tumors and could thus be of use in the treatment of cancer.

The investigators who discovered the protein involved in blood vessel growth are also studying the relationship of oxygen to the healing process. It is well known that wounds heal better and resist infection more effectively if their blood and oxygen supplies are good. However, in the past there has been no satisfactory way of measuring oxygen supply to tissues. This research team has now patented a simple device for measuring oxygen tension in human tissue. The device, which resembles an intravenous needle, has been used in several hundred patients and has proved to



be extremely valuable in deciding when blood transfusions are necessary. Studies utilizing the device have shown that exposure of guinea pigs to high levels of oxygen, especially during the first 4 hours after infection, greatly increased the animals' ability to retard bacterial growth.

### **Pharmacological Sciences**

Pharmacology, the study of therapeutic drugs and other biologically active compounds, is increasingly making use of knowledge and techniques from other basic sciences, including genetics and molecular biology. Sophisticated new tools, such as recombinant DNA and monoclonal antibody technologies, are contributing to the progress of research in this field. Discoveries in the pharmacological sciences, in turn, often lead to a better understanding of fundamental cellular and physiological processes.

The NIGMS Pharmacological Sciences Program supports research ranging from the synthesis of chemicals and natural products that have biological effects to investigations of drug actions in humans. The program also funds studies related to the mechanisms of action of anesthetics and muscle relaxants. Support of research in basic chemistry forms an important portion of the program's portfolio. This research in turn assists in the design, synthesis, and structural analysis of a wide variety of compounds of potential practical use. NIGMS grantees working in this area are involved in designing model compounds that give them information about the structure and function of catalytic sites on enzymes, in synthesizing artificial enzymes, and in synthesizing and characterizing specific enzyme inhibitors.

One very active area of pharmacological research involves basic studies of the cytochrome P-450 system. This enzyme system, which is crucial to detoxifying foreign substances and metabolizing drugs, also appears to be involved in the normal metabolism of many

substances, including cholesterol, fatty acids, prostaglandins, bile acids, and steroid hormones. Moreover, cytochrome P-450 enzymes have been found in bacteria, yeast, plants, insects, and vertebrates, and therefore represent a class of proteins that have been conserved during evolution. Increased knowledge about this important family of enzymes will help scientists understand how an organism responds to foreign compounds, including many cancer- and mutation-causing agents. In addition, such research may facilitate the design of more effective drugs and insecticides.

Studies of the role of the cytochrome P-450 system in drug metabolism have also allowed investigators to understand the variability—often genetically based—in people's response to drugs. For instance, scientists have discovered that the Japanese metabolize the anticonvulsant drug mephenytoin more slowly than do otherwise similar Caucasian populations. This results in higher blood levels of active drug that last for longer periods, requiring a downward adjustment of dose. Given the fact that pharmaceutical companies frequently test new drugs in selected populations but ultimately market those drugs worldwide among many different racial and ethnic groups, there is a profound need for further studies on such variability in drug metabolism. This research should lead to the development of safer new drugs, as well as to the protection of specific subpopulations from the potential side effects of those drugs currently in use.

Another major thrust of the basic research supported by the Pharmacological Sciences Program involves determining how pharmacologically active substances exert their effects, so that adverse reactions can be minimized and new and better drugs can be developed. Part of this effort relates to the elucidation of the structure of particular compounds that have been found to be useful as drugs. Once a structure has been defined, it can be modified in attempts to design more potent drugs, drugs with the desired

therapeutic action but not the side effects, or drugs to which organisms have not yet developed resistance.

An example of this process is the development of beta-lactam antibiotics, which include the penicillins and the cephalosporins. Naturally occurring beta-lactam antibiotics were discovered many years ago and currently are among the most widely used antibiotics. Many tons are manufactured annually by the drug industry, generally by isolating specific compounds from fermentation broths and then chemically modifying them to yield the desired characteristics. Scientists are continually searching for new, structurally different beta-lactam antibiotics, because bacteria are rapidly developing resistance to those that are traditionally prescribed. Recently, an NIGMS grantee discovered a totally new approach to beta-lactam synthesis. The chemical reaction he uses is very versatile and proceeds at room temperature under mild conditions. After further research, when this process is fully developed, it could be of profound utility in the creation of completely new classes of beta-lactam antibiotics.

Other Pharmacological Sciences Program grantees are actively investigating factors that can influence drug action, including interactions with other medications. One of these studies is focusing on the corticosteroids, a class of powerful compounds (in the form of naturally occurring hormones or synthetic chemicals) used in the treatment of arthritis and other inflammatory disorders, asthma, allergies, shock, and tissue rejection following organ transplantation. Although corticosteroids—which include prednisone, cortisone, and dexamethasone—are among the most frequently used medicines, there are major gaps in our understanding of their varied actions and effects. Physicians do not even have good guidelines on the proper dosage, so they must rely on past experience with similar patients in selecting a starting dose, and then on trial and error in tailoring the amount of drug needed to treat a specific patient's symptoms.



Despite their many benefits, corticosteroids can cause a number of adverse reactions, some of them quite severe. The incidence of these side effects is directly tied to the size of the dose and the length of drug therapy. Clearly, any means of calculating the smallest amount of corticosteroid that will be effective in the shortest period of time could improve the use of this important class of drugs while significantly reducing adverse reactions. A major step in this direction is being taken by an NIGMS grantee who is looking at the basic mechanisms involved in the body's absorption, distribution, metabolism, and excretion of corticosteroids. Recognizing that age, various diseases, and the concurrent use of other medicines can alter the drugs' effects, he is examining many of these variables to develop a detailed model of corticosteroid action.

One of this investigator's findings is that certain antibiotics, oral contraceptives, and anticonvulsant drugs can alter the time it takes for the body to break down and eliminate corticosteroids. For example, a person who is taking corticosteroids to treat asthma will require a lower dose to control the disease if he or she is also taking antibiotics such as erythromycin or troleandomycin. The same is true for women who use oral contraceptives. Anticonvulsants, on the other hand, speed steroid metabolism, so a given steroid dose remains in the body for a shorter period of time than it might otherwise and thus has a reduced therapeutic effect.

Several researchers supported by the Pharmacological Sciences Program are concerned with how to deliver drugs to specific sites in the body more rapidly and with greater precision than is now possible, thereby reducing side effects caused by the drugs' unintended action on other organs and tissues. One approach some of these scientists have taken is to use microscopic "capsules," called liposomes, to carry the drugs. Liposomes are simply membranes composed of fatty substances surrounding a watery

compartment into which a variety of molecules can be inserted. They are nontoxic and biodegradable.

Placing therapeutic agents in liposomes confers several advantages over compounds not encapsulated in this way. In addition to having features that make it possible to direct them to specific cell types, liposomes are able to release their contents more gradually and over a longer period of time, the contents are protected from too-rapid breakdown or excretion by the body, and a lower dose of medicine may thus be required. Liposomes have already been used with some success to convey anticancer drugs to tumor cells, while sparing normal cells from the drugs' devastating effects.

For the past 4 years, an NIGMS grantee has studied the physical and chemical factors that influence the effectiveness of liposomes as drug carriers. He has found that by modifying liposome composition, size, and dose he can alter the rate and site of uptake of the liposomes by target cells. In the course of this work, he and his colleagues devised a means for evaluating the effects of future liposomal modifications on the success of targeted drug delivery.

Another NIGMS-supported investigator has used liposomes in a different way. He and his colleagues developed prototype artificial red blood cells composed of liposomes encapsulating hemoglobin. The artificial cells, which he calls neohemocytes, may have important advantages over previous attempts to produce artificial blood. Since the neohemocytes are substantially smaller than real red blood cells, they should be able to pass freely through normal, and possibly moderately constricted, small blood vessels such as capillaries. Because the artificial cells lack blood group antigens and have a shelf life of 6 months, the researchers hope they will be useful in the treatment of trauma patients, as a temporary substitute for whole blood transfusions, and in the treatment of tissue ischemia (localized loss of blood supply).

The Pharmacological Sciences Program supports the bulk of the basic

research in chemistry, particularly organic chemistry, funded by NIH. According to a recent National Academy of Sciences study on opportunities in chemistry, basic studies in this area "will help future generations to cope with their evolving needs and unanticipated problems." The report goes on to state that "no area of basic science . . . offers a more secure investment in the Nation's future."

NIGMS grantees have made many advances in basic chemistry research over the past few years. For example, one researcher recently developed techniques for synthesizing essentially pure forms of a particular class of compounds, a feat not previously possible. This enables him to produce an active, therapeutic agent without the related, inactive or even toxic compounds that are produced in most complex chemical reactions. The new method has tremendous commercial implications, because it is relatively inexpensive and uses materials that are widely available in nature to minimize unwanted drug side effects.

The research of two long-time grantees was recently identified in a report by the National Science Board on the state of U.S. science, engineering, and technology as being among eight "recent and significant achievements of scientific and engineering research." Both scientists are involved in efforts to design a variety of artificial molecules with the catalytic properties of natural enzymes. One of the investigators has approached this by creating molecules with cavities that bind target substances and that have chemical groups arranged in such a way that they speed up the rate of a specific reaction in the bound substance. The other has taken cavity-containing molecules and chemically modified them so they approach the catalytic power of natural enzymes. While these efforts are still fairly preliminary, they hold a great deal of promise for eventually enabling scientists to develop artificial enzymes that function with an efficiency approaching that of enzymes found in nature and that have specific medical and technological uses.



*Space-filling model of a cavity-containing molecule developed by an NIGMS grantee.*

## Research Training

The training activities of the NIGMS research programs, together with three special training efforts—Minority Access to Research Careers, the Medical Scientist Training Program, and the Pharmacology Research Associate Program—form a vital part of the Institute's mission. Broad, multi-disciplinary predoctoral training programs provide a solid foundation of knowledge in the basic biomedical sciences to highly qualified students. This experience prepares them to pursue research careers in a wide variety of areas, many of which reflect the scientific fields covered by other NIH Institutes. Postdoctoral training emphasizes research related more directly to the Institute's programs, particularly basic research training for those with a professional degree.

The MARC Program was established in 1975 to address the underrepresentation of blacks and other minority groups in scientific fields. According to the Ford Foundation, minorities constitute more than 20 percent of the Nation's college-age population, but they accounted for only 8 percent of the Ph.D.'s awarded in 1983. Blacks, Puerto Ricans, Mexican Americans, and American Indians together accounted for just over half of this total. The problem is even more serious in the biological sciences. U.S. Department of Education statistics indicate that blacks and Hispanics received 9.6 percent of the bachelor's degrees awarded in the biological sciences in 1981. However,

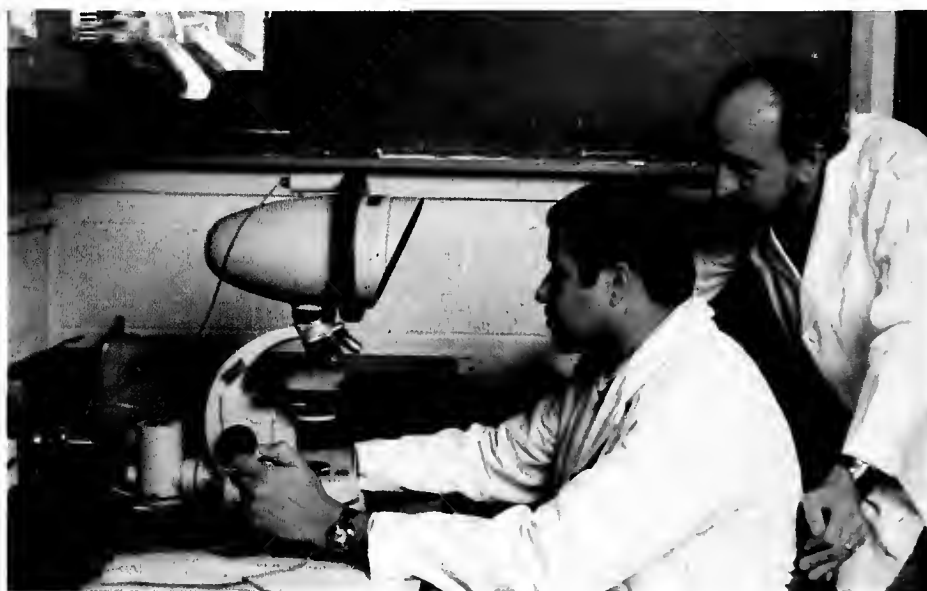
in the following year these groups constituted only 4.5 percent of full-time graduate students in the biological sciences.

It is evident that minority group members are underrepresented at all stages of the scientific career, but the disparity widens considerably after the receipt of a bachelor's degree. A recent study by the Institute of Medicine of the National Academy of Sciences found three factors primarily responsible for the increasing racial disparity as students move from undergraduate to graduate education: differences in the structure of opportunities, differences in student aspirations, and differences in student preparation. With regard to opportunities, minority students often do not benefit from the institutional reputations and informal networks available to students in major research institutions. With regard to aspirations, a lack of information and encouragement and a shortage of role models may work against the minority student. With regard to preparation, minority students may not receive the same levels of laboratory exposure, research experience, and faculty supervision that students in other schools receive.

The MARC Program hopes to reduce these disparities by providing

special research training opportunities and incentives in the biomedical sciences to attract and retain minority students who have the potential for a research career. Several recent studies of the MARC Program have confirmed prior anecdotal evidence that it is meeting its goals. The latest study, conducted by the Institute of Medicine, focused on one component of MARC, the Honors Undergraduate Research Training Program. It found that an increasing number of students at minority institutions that receive MARC support are majoring in science fields, going on to graduate school, and ultimately finding work in science. Overall, the program has produced a new awareness among minorities of the opportunities available in biomedical research and has provided the means to take advantage of these opportunities.

The Medical Scientist Training Program, which just celebrated its 20th anniversary, was created to help alleviate the critical shortage of highly skilled clinical researchers. Since the standard course of study at most medical schools cannot by itself provide the experience necessary for individuals to become researchers, this program combines training for the M.D. degree with the extensive research experience



*Scientists supported by the NIGMS Minority Access to Research Careers Program.*

needed to help physicians become clinical investigators. The program is meeting its objectives, as evidenced by a recent evaluation which indicated that well over two-thirds of those who received the combined degree 5 or more years ago are now involved in academic pursuits.

The Pharmacology Research Associate Program seeks to develop leaders in pharmacological research for key positions in academic, government, and industrial research laboratories. It is a small intramural program for which 11 recently trained scientists are selected each year for a 2-year period of postdoctoral research under the direction of senior researchers at NIH and the Alcohol, Drug Abuse, and Mental Health Administration. It is intended for promising scientists who have made a commitment to research in the pharmacological sciences, as well as for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in pharmacological research. In its first 20 years, from 1965 to 1985, the program trained 189 scientists, 90 percent of whom have since entered research careers.

### **The Future**

Biomedical science is just beginning to feel the impact of the major breakthroughs made in the last decade. Tremendous progress is being made toward the treatment, cure, and—most important—prevention of major diseases. As Dr. Lewis Thomas wrote in an essay in the September 1985 issue of *Discover* magazine: "As we develop new, decisive technologies that are based on a really deep understanding of disease mechanisms, my guess is that they will turn out to be relatively inexpensive compared with the kinds of measures that medicine is obliged to rely on these days for just making do. . . . It will make an enormous difference to the practice of medicine if we can keep the basic biomedical science going and keep it coupled as congenially as possible to clinical research. We shouldn't forget how useful medicine can be when

its scientific base becomes really solid and effective." NIGMS will continue to support high-quality basic biomedical research and the training of future researchers so as to amplify and strengthen the body of knowledge that underlies medicine—knowledge that will ultimately permit specific diseases to be conquered.

## **The Biennial Report of the Director, National Institute of Child Health and Human Development**

### **History**

The following events represent milestones in the development of the National Institute of Child Health and Human Development (NICHD).

- January 12, 1961—The report of President-elect Kennedy's Task Force on Health and Social Security called for establishing a National Institute of Child Health within the NIH.

- February 17, 1961—A Center for Research in Child Health was established by the Surgeon General in the Division of General Medical Sciences.

- October 17, 1962—Public Law 87-838 authorized the Surgeon General, with the approval of the Secretary, to "establish in the Public Health Service an institute for the conduct and support of research and training relating to maternal health, child health and human development, including research and training in the special health problems and requirements of mothers and children and in the basic processes of human growth and development, including prenatal development."

- January 30, 1963—The Secretary of HEW approved establishment of the NICHD, with provision that the Center for Research in Child Health be transferred from the Division of General Medical Sciences to the new Institute.

- October 31, 1963—P. L. 88-164 authorized funds for the construction of centers to conduct research on mental retardation and related disabilities. (The NICHD continues to provide support to centers conducting research in mental retardation, although the authority to construct new centers expired June 30, 1967.)

- November 14-16, 1963—The first meeting of the National Advisory Child Health and Human Development Council was held.

• December 2, 1965—A major NICHD reorganization gave emphasis to four program areas: reproduction, growth and development, aging, and mental retardation.

• April 18, 1967—A second reorganization of the NICHD acknowledged the Institute's intramural programs by separating responsibility for intramural and extramural research and creating seven intramural laboratories.

• August 9, 1968—The Center for population Research was established within the NICHD. The Center is responsible for contract and grant programs in population and reproduction research and has been designated by the President as the Federal agency with primary responsibility for population research and training.

• December 24, 1970—P.L. 91-572 added Title X to the Public Health Service Act which in part authorized the conduct and support of research in family planning and population problems. The research authority was delegated to the NICHD and administered by the Center for Population Research.

• April 22, 1974—P.L. 93-270 directed the Secretary to carry out, through the NICHD, research on sudden infant death syndrome (SIDS) and report on it to the Congress.

• May 27, 1975—The Center for Research for Mothers and Children was established. It is the Federal Government's focal point for research and training on the special health problems of mothers and children, with responsibility for increasing knowledge about pregnancy, infancy, childhood, adolescence, and adulthood, and for administering grant and contract programs related to these areas.

• June 30, 1975—The Adult Development and Aging Branch and the Gerontology Research Center, with their programs for support and conduct of research in the field of aging, were transferred from the NICHD to the new National Institute on Aging.

• August 13, 1981—P.L. 97-35 removed the requirement that Title X of the Public Health Service Act be the sole authority for population research appropriations.

• October 1981—The Institute published "Child Health and Human Development: A Five-Year Research Plan" to guide the research programs conducted and supported by the Institute.

• November 1983—The Infant Mortality/Low Birthweight Initiative was introduced emphasizing identification of the causes of intrauterine growth retardation and premature labor and assessing methods for treating and preventing these conditions.

• November 1984—The Contraceptive Development Initiative was introduced with the aim of developing new contraceptives and assessing the safety, effectiveness, and acceptability of new and previously developed contraceptive methods as a means of reducing unintended pregnancy.

• November 20, 1985—P.L. 99-158 directed the NICHD to appoint an Associate Director for Prevention "to coordinate and promote the programs in the Institute concerning the prevention of health problems of mothers and children."

• 1986—Dr. Duane F. Alexander was appointed Director of the Institute.

## Introduction

The mission of the National Institute of Child Health and Human Development is to help families have healthy children at the time they are wanted, to prevent disease and disability among children, to foster normal development early in life, and to ensure that every child has the opportunity to fulfill his or her potential for a healthy and productive adulthood. In pursuit of its mission, the NICHD supports programs focused on the reproductive, developmental, and behavioral processes that determine the health of children, adults, families, and populations. By increasing our knowledge in these areas, the Institute is contributing to a healthier, more productive life for all.

The programs supported by the NICHD consist of multidisciplinary research, research training, and public information efforts focused on maternal, child and family health, and on related population changes. Research in the reproductive sciences develops knowledge enabling men and women to regulate their fertility and overcome problems of infertility. Research for mothers, children and families advances knowledge of fetal development, pregnancy, and birth; identifies the prerequisites of optimal growth and development throughout infancy, childhood, and adolescence; and contributes to the prevention and amelioration of mental retardation. Research in the behavioral sciences increases our understanding of the social and psychological factors that influence health and development.

Thus, through its broad range of biomedical and behavioral programs, the NICHD strives to gain the knowledge which will enable it to prevent disease and disability in the early years of life. Improving the health of our children builds a healthier future for all.

## Health Problems Addressed by the National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development is responsible for research that addresses one of the most important issues in health today—the prevention of disease and disability to improve the health and functioning level of the future adult population of the United States. Successful achievement of the Institute's program goals will decrease the burden of disease and disability in children and adults and have a major effect on reducing health care costs for the Nation.

The Institute's research is directed toward preventing infant mortality and childhood morbidity, as well as toward permitting couples to fulfill their reproductive choices. Each year, nearly 40,000 babies die before their first birthday and another 200,000 are born with or develop mental or physical defects. Approximately seven million people in the

United States are retarded, and 20 to 25 million citizens live in families in which there is a retarded person. Learning disabilities affect an estimated 15 percent of the U.S. school-age population and injuries now affect more children, adolescents, and young adults than do illness or disease. Obesity, which affects 25 to 45 percent of the adult population, often has its antecedents in childhood. One out of seven American couples are infertile, while more than three million pregnancies in the United States each year are unintended, including nearly one million among teenagers.

Each of these major public health problems is addressed by the research programs of the NICHD. The knowledge gained by the Institute has applicability to a wide range of developmental problems, diseases, and handicaps. The NICHD research will continue to pursue the goals of having each child wanted, improving the outcome of pregnancy and infancy, preventing or remediating disability, and fostering normal development and healthy adulthood.

### Research Progress

The NICHD has one of the broadest research missions of any of the Institutes at the NIH. In FY 1985, the Institute carried out its mission through the support of grants and contracts and the conduct of research in its laboratories on a wide range of biomedical and behavioral research studies. During this period, several major achievements were reported by NICHD-supported scientists.

### Vaccine Development

Perhaps the most timely advances were made by intramural scientists in the area of vaccine development. Whooping cough, typhoid fever, and meningitis due to *Hemophilus influenzae* are still responsible for illness, death, or permanent disability in many children. In the case of whooping cough (pertussis), fear of side effects from the existing vaccine made from whole bacteria is inhibiting its use, resulting in an increase in the number of cases of this



*An early step in developing vaccines is to make certain that they are not toxic to cells in culture.*

disease. Intramural scientists at the NICHD recently have isolated and purified the single component of the pertussis organism that they believe is sufficient to produce an entirely safe and effective vaccine. They are about to start field trials of the new vaccine in Sweden, where pertussis has reached epidemic proportions without the use of vaccine.

These same intramural scientists have also been successful in developing new vaccines against typhoid fever and *Hemophilus influenzae* type B. The new typhoid vaccine, just entering field trials in India and Nepal, is inexpensive, is expected to have minimal side effects, and to produce lifelong immunity. Despite effective antibiotics, *H. influenzae* remains a serious cause of sickness and death in infants and is a leading cause of acquired mental retardation in this country. A recently licensed vaccine based on earlier work of these NICHD scientists is effective in older children but not in those under 2 years of age, the time of greatest risk. These investigators have now produced a modified vaccine that binds the *H. influenzae* antigen to substances that augment immunity.

Studies of this vaccine in infant monkeys have been successful, and the Institute will soon begin a field trial in human infants.

### Birth Defects

Birth defects and genetic disorders have long been recognized as major contributors to infant mortality and lifelong morbidity but have been unusually difficult to approach experimentally. This situation is now changing due to the new research tools provided by molecular biology. For example, an investigator is using monoclonal antibodies and cDNA probes to understand abnormal development of cartilage as part of the larger question of abnormal limb development.

NICHD scientists have discovered that an embryo's first proteins form the "bones" of a cell. These thread-like proteins, called cytokeratins, run through the cell's interior helping the cell to keep its shape. Because cytokeratins arise in embryonic cells destined to become skin, this tissue appears to be among the first to specialize during development. Identifying genes and proteins active only in the embryo will facilitate the

search for unique molecular signals that control embryo development and will be an important step forward in identifying the causes and discovering treatments or methods to prevent birth defects.

### **Smoking and Pregnancy**

The deleterious effects of smoking on birth weight have been well documented. Now a new NICHD-supported study has provided evidence that smoking is also a factor in prematurity. In a study of more than 36,000 women, it was found that pregnant smokers were 20 percent more likely to deliver more than 3 weeks early. Even more critical is the finding that women who smoked one or more packs of cigarettes a day were 60 percent more likely to deliver 8 or more weeks early compared to non-smokers. It was found that the number of babies born 8 or more weeks early would decrease by 8 percent if all pregnant women were to quit smoking.

### **Research Benefiting Children**

In 1985, the Food and Drug Administration (FDA) approved the marketing of synthetic growth hor-

mone. The NICHD participated in the clinical trials which led to this step. Previously human growth hormone was available only from the pituitary glands of cadavers. This supply was inadequate to treat the hundreds of thousands of children in this country who are extremely short for their age. Now that the synthetic growth hormone is available, there will be a sufficient supply to meet the needs of children as well as for research purposes.

Another exciting recent advance is the development of a home computer program that can be used by diabetic adolescents for the management of their disease. This development is important because diabetes treatment in young patients often must be adjusted daily and most adolescents rebel against this tight regimen. By involving the young patient more in the control of his own treatment, control of diabetes in adolescents has been facilitated, and family stress that often accompanies this disease has been reduced.

### **Progress in the Population Sciences**

NICHD scientists have isolated and characterized a protein produced in the gonads that appears to block a hormonal step necessary for the development of sperm and egg cells. Because the protein, called inhibin, blocks this step without upsetting the body's hormone balance, it may lead to improved birth control pills for women and provide the basis for a hormone contraceptive for men. Inhibin may also constitute a missing link in knowledge about the mechanism that precisely orchestrates secretion of other reproductive hormones.

As part of the Institute's contraceptive evaluation program, other NICHD-supported scientists have reported findings concerning the safety of three current methods of family planning: (1) young women who have used oral contraceptives are at no greater risk of developing breast cancer before menopause than are women who have never used them; (2) women who have used IUDs are more likely than other women to become infertile, although the copper-bearing devices are the least likely to cause such problems; and (3) women who use contraceptive spermicides and unintentionally become pregnant have no greater chance of producing a premature or low birth weight (LBW) infant or an infant with a birth defect than do women who become pregnant while using other types of contraceptives.

Other NICHD researchers have found a possible explanation for the doubling of the incidence of ectopic pregnancy that has occurred in the United States in the past decade. Ectopic pregnancy almost always results in the death of the fetus and is a life-threatening situation for the mother as well. A team of investigators supported by the NICHD has discovered a probable cause to account for at least some of this increase: vaginal douching. In a recently reported study, it was found that women who use a commercial douche at least once a week were more than four times as likely as women who never douche to have an ectopic pregnancy. It was also found that vaginal douching



*Doctor measures child in growth hormone study (this child is a normal volunteer).*



may increase the risk of pelvic inflammatory disease which is known to predispose women to ectopic pregnancies and infertility.

### Research Objectives

Since its inception in 1962, a basic premise of the Institute has been that preventing the onset of problems during fetal development, infancy and childhood is the key to ensuring a healthy and productive adulthood. Prevention is such an integral part of the Institute's research program that of the 15 prevention priority areas identified in the 1990 National Prevention Objectives of the Department of Health and Human Services (DHHS), the NICHD is the lead agency in two (pregnancy and infant care and family planning) and has substantial involvement in 11 other areas. In the past 2 years, 40 percent of the Institute's budget has been allocated to prevention research. Thus, the requirement imposed by P.L. 99-158 that the NICHD appoint an Associate Director for prevention is a legislative affirmation of the Institute's commitment to the principle of prevention.

This commitment is exemplified by three areas of research in which opportunities now exist to make great strides toward preventing infant mortality, unintended pregnancy, and developmental neurological problems. The Institute has designed a major research initiative in each of these areas and has placed top priority on supporting research that addresses the goals of each initiative.

#### Infant Mortality/Low Birth Weight Initiative

The international ranking (15th) in infant mortality currently experienced in the United States is not in keeping with its commitment for a healthy society and is attributable almost entirely to low birth weight. Low birth weight, defined as birth weight less than 5½ pounds, is associated with two-thirds of all infant deaths. Thus, it is the preeminent problem in child health in the United States today. These infants often require intensive care and



*A nurse feeds breast milk through a tube to a baby girl born 2 months prematurely. At 3 weeks of age, she weighs 3 pounds, 13 ounces.*

experience a high incidence of illness and complications. The very low birth weight (VLBW) infants (less than 3½ pounds) face even greater hazards. The risk of these babies dying during infancy jumps 200 fold over normal weight babies and those who survive face a much greater risk of developing lifelong disabilities such as mental retardation, cerebral palsy, seizures, learning problems, blindness, and deafness. The incidence of such handicaps in VLBW children is more than 50 percent at school age. To address this problem, the NICHD has implemented a special research initiative focused on the prevention of low birth weight and infant mortality.

This initiative involves extramural, epidemiological, and intramural efforts to reduce infant mortality by developing new knowledge (basic and clinical) related to the causes of low birth weight and its prevention. The initiative places particular emphasis on identifying the causes of intrauterine growth retardation (IUGR) and premature labor and on assessing methods for treatment and prevention of these conditions.

Implementation of the initiative began in 1985 with the funding of

several projects focused on reducing infant mortality and low birth weight. During the year, the NICHD funded two new Perinatal Emphasis Research Centers, one focusing on the physiology and pathophysiology of IUGR and the other on intra-uterine fetal growth and metabolism.

Scientists working in these two centers will explore the biological mechanisms that control fetal growth and how these processes go awry to produce IUGR. Over the next 5 years, multidisciplinary teams at each center will approach the problem of IUGR from different angles—studying physiological, hormonal, and nutritional influences.

Two new research networks to evaluate treatments used in prenatal and neonatal care were funded during FY 1986. The two networks, one comprised of neonatal intensive care units, the other of maternal-fetal medicine units, will permit a faster, more effective system for evaluating treatments currently used to combat a variety of prenatal and newborn health problems. Investigators from each unit and from the NICHD will first identify major problems in obstetrics and neonatal care that are

appropriate for clinical studies and set up research protocols to study them. Over the next 5 years, the researchers in each network will evaluate old therapies, modify existing therapies to improve their effectiveness and safety, and try new therapies in carefully controlled studies. Using this type of system, the most effective treatment can be applied quickly to ameliorate or prevent many of the health problems in pregnancy and the newborn infant. Once the best solution to a problem is identified, the researchers expect private physicians and hospitals to adopt the treatment quickly. Fourteen U.S. medical centers comprise the two networks.

In addition, a clinical trial investigating the relationship of vaginal infections to prematurity was initiated with the recruitment of 7,000 out of an eventual 15,000 pregnant women who will be screened for the presence of certain microorganisms which may be associated with preterm labor. Those women found to have the microorganisms will be treated to determine whether the organisms can be eliminated and whether doing so reduces LBW and preterm labor. Also, the Better Babies Project was designed and initiated in Washington, D.C., to determine whether identifying low income women early in their pregnancies and linking them to medical and social services can reduce low birth weight.

The Institute's priorities also include conducting targeted efforts in the areas of the biochemistry of labor and the premature rupture of membranes and initiating a clinical trial to assess the value of routine obstetric ultrasound screening in detecting and managing intrauterine growth retardation.

In addition to low birth weight and prematurity, other causes contribute to the infant mortality rate. The NICHD supports an intensive research effort in the areas of sudden infant death syndrome (SIDS) and of birth defects and genetic diseases.

### **Contraceptive Development Initiative**

The NICHD has proposed a second research initiative for FY 1986-89 that focuses on contraceptive development and reducing the number of unintended pregnancies. It places emphasis on four major areas: (1) basic biomedical research in human reproduction; (2) development of new contraceptive methods; (3) studies of the safety and effectiveness of contraceptive methods to determine whether they are appropriate for widespread use; and (4) research on the behavioral aspects of contraceptive use.

In the United States, women report that more than half of all pregnancies are unintended—that is, either unwanted or ill-timed. This means that of the six million pregnancies occurring annually, over three million are unplanned, and about half of these (1.5 million) are terminated by legal abortion. Many unplanned pregnancies result in illegitimate births, which now account for one in five births. The high incidence of unplanned childbearing has adverse effects on the health of mothers and children and on the ability of families to maintain economic independence. The problems associated with unplanned childbearing are most severe among very young women and among people living in poverty, although the impact is perceptible at all socioeconomic levels.

Recent surveys show a close relationship between the health of the baby and whether or not the mother wanted to become pregnant. Not surprisingly, women with unwanted pregnancies report that they first obtain prenatal care later in pregnancy than those who wanted to become pregnant. Furthermore, among the births resulting from unintended pregnancies in the United States during 1979-82, the prevalence of low birth weight was significantly greater than among planned births. Thus, efforts to help couples avoid unintended pregnancies will complement and enhance the Institute's efforts to reduce the incidence of low birth weight and to improve the health of mothers and children.

Of the 47 million sexually active women of reproductive age in the United States, about 95 percent use some form of contraception some of the time. However, there is a wide gap between their fertility aspirations and outcomes, much of it due to ineffective and episodic contraception. In addition, there is fear and confusion in the minds of many couples about the safety of various contraceptive methods.

No currently available contraceptive is fully satisfactory. In order to improve voluntary regulation of fertility and reduce the proportion of unplanned pregnancies, an array of methods that are safe, effective, inexpensive, easy to administer and acceptable to various population groups must be available. Although no new funds were appropriated to support this initiative, research began using available funding, and progress has been made in several areas. The discovery of the structure of inhibin, which appears to block the development of sperm and egg cells, and the clarification of the function of follicular regulatory proteins have been particularly important to the chemical characterization, synthesis, and clinical application of new reproductive peptide hormones. Three universities are receiving support to conduct research on providing contraception by preventing the maturation of eggs and sperm. A new project has been funded that will transfer research findings and technological developments from investigators working with the hormone known as human chorionic gonadotropin to Institute-supported centers conducting research on the receptors of ovulatory hormones. This sharing of information will assist investigators seeking a contraceptive based on blocking the ovulatory hormone receptors. Three contracts have been funded to support research on new spermicides and methods for administering them. Two contracts have been awarded to support the development of a long-acting skin patch for delivering contraceptive drugs.

Future plans for the Contraceptive Development Initiative call for: (1) expanded studies of inhibin; (2) expanded studies of immunocontraception, new peptide hormones, and identification of vulnerable steps in the reproductive process; (3) new behavioral studies on early child-bearing to understand unintended pregnancy in adolescents; (4) clinical studies with a long-acting (24-hour) spermicidal formulation; (5) new and expanded studies of the safety and efficacy of contraceptive methods; and (6) new and expanded studies on the acceptability and utilization of contraceptive methods.

### **Molecular and Developmental Neurobiology**

Neurobiology is the most recent area to receive increased emphasis in the NICHD. High priority has been accorded to research in this area in response to developments in molecular and developmental neurobiology that now offer numerous promising opportunities to advance our understanding of normal neurological development and congenital neurological malfunctions.

A workshop held in February 1985 brought together 35 investigators representing molecular genetics and developmental neurobiology. Their discussions highlighted the methodological and theoretical advances in four main areas: cell lineage, neuronal migration, axonal guidance, and long-range connectivity and synaptogenesis.

Advances include research conducted in the NICHD Laboratory of Developmental Neurobiology where significant progress has been made toward understanding the relationship between environmental stimuli and the development of the nervous system. Using a culture model of the mammalian central nervous system, it has demonstrated for the first time a direct relation between glia, neurons, and electrical stimuli. Researchers in the Institute's Laboratory of Comparative Ethology are studying what appear to be genetically determined differences between individuals' physiological and behavioral responses to novelty and challenge in the environment. These studies have the potential for

increasing understanding of childhood behavior and behavioral disorders, as well as the methods by which these disorders may be prevented or treated. They may also shed light on the question of whether individuals at high risk for anxiety disorders also have a tendency toward cardiovascular or other somatic abnormalities. A better understanding of these conditions in childhood will lead to a better understanding of the factors contributing to adult conditions such as depression, addictions, and the full range of psychopathology.

Progress in the availability of research resources has increased opportunities in the area of neurobiology. A repository of human DNA probes and libraries has been established which one day will provide investigators with molecular clones representing the entire human genome. In addition, a monoclonal antibody bank has been established that will provide known and newly developed antibodies to researchers in the field of limb development and other areas of developmental biology. Furthermore, two new animal models are being developed for studies of neural tube defects.

### **Research Opportunities**

The following examples illustrate the exciting research opportunities that exist throughout the programs of the NICHD.

#### **Infant Mortality**

##### *Sudden Infant Death Syndrome*

Once infants are out of the critical newborn period, Sudden Infant Death Syndrome is the leading cause of death up to 1 year of age. Annually in the United States, more than 6000 babies die of SIDS. The NICHD, which has primary Federal responsibility for research on the Sudden Infant Death syndrome, recently completed a large cooperative epidemiologic study of SIDS, which, among other findings, provided clear evidence that DPT immunization is not linked to SIDS. The exact etiology of SIDS, however, remains elusive. Over the years

much work has been done on a wide range of biologic, epidemiologic, and behavioral research in SIDS. Now, there is concern that scientists in the SIDS field have become discouraged by the lack of positive findings. As a priority, therefore, the Institute is determined to rekindle new efforts and approaches to research in SIDS and has issued a Request for Grant Applications on SIDS encouraging investigators to focus efforts on neural control of cardiorespiratory function, particularly at the brainstem level. In addition, the Institute will convene (September 1986) a consensus development conference on Infant Apnea and Home Monitoring. Materials presented at this meeting should clarify the relationship, if any, between apnea and SIDS, and determine whether and under what circumstances monitors are useful in the treatment of infantile apnea.

##### *Birth Defects and Genetic Diseases*

Birth defects and genetic disorders are a major contributor to infant mortality and lifelong morbidity. The field of developmental neurobiology has arrived at a point where numerous opportunities exist to advance our understanding of congenital neurological malfunctions. Among the most promising opportunities



*Photo shows scientist at microscope performing gene transfer technique. Investigators are working to identify the causes of genetic diseases and birth defects, through basic research in cells and animals. Discoveries of how genes control physical development offer hope for preventing certain genetic diseases.*

are: (1) studying the nature and mechanism of action of cell recognition of cell adhesion molecules; (2) analyzing the extracellular molecules that may be involved in axonal guidance and regulation of neuronal morphology; (3) performing molecular analyses of the genes for the newly discovered, soluble factors that specify neuronal phenotype; and (4) analyzing the interaction between developmental signals, and the patterns of electrical activity imposed on the nervous system by the environment.

## Childhood Morbidity

### *Mental Retardation*

Mental retardation is a lifelong problem and a major health and social issue, with multiple causes that require study of the full range of developmental variables. As such, it exemplifies the multidisciplinary mission of the NICHD. Mental retardation affects millions of Americans and leads to annual public expenditures (Federal, state, and local) of billions of dollars.

Mental retardation can be caused by a complex of biological, psychological, and social determinants. Genetic factors, metabolic disorders, and prematurity or other disturbances during pregnancy are a few of its biological determinants. Infection or injury at birth or in early childhood may also underlie mental retardation. In addition, lack of stimulation, inadequate educational opportunities, and generally deprived living conditions may be causal or contributory factors. The moderate and more severe conditions of retardation usually can be traced to faulty genes, infections, accidents, diseases, and disorders that cause brain damage.

Much of the Nation's research on mental retardation is conducted in a network of congressionally established Mental Retardation Research Centers supported by the NICHD. Studies in the biomedical sciences supported by the Institute have led to interventions that are highly effective in preventing mental retardation resulting from a few of the many biological causes, such as congenital

hypothyroidism. NICHD-supported studies applying the behavioral sciences to the much larger category of sociocultural-familial mental retardation have suggested that early behavioral interventions may be effective in reducing the likelihood of mental impairment in high-risk infants and children.

Major advances have been made in investigators' ability to study normal and abnormal development of the brain and nervous system, where looking for the underlying causes of much of the mental retardation that remains of unknown origin must be done. The new tools of molecular biology are being applied to the possibility of diagnosing and eventually preventing mental retardation due to genetic defects.

Significant opportunities in mental retardation research include: the use of new biologic systems and tools to study Down syndrome (Trisomy 21); studies to identify specific non-genetic intergenerational influences on mental retardation and other learning disorders; investigations of behavioral abnormalities which may result from lower, nonmalforming doses of chemical and environmental agents capable of producing malformations; research to identify infants at risk for mental retardation; and research to help parents and communities integrate mentally retarded children and adults into the mainstream of modern American life.

### *Learning Disabilities*

The NICHD supports a research effort focused on basic developmental biology, behavioral biology, learning and cognition, perception, and memory as they relate to children and adolescents with learning disabilities. Studies of the learning processes in nondisabled children serve as a standard against which the difficulties in the acquisition of academic skills by children with disabilities can be measured.

Other NICHD research in this area includes the long-term consequences of learning disabilities, the role of computers in the diagnosis and treatment of learning disabilities, and the use of molecular biology techniques and quantitative genetic methods to investigate the

role of heredity in several types of learning disabilities. Furthermore, studies of brain activity and brain structure are in progress to determine their potential as methods for diagnosing learning disabilities.

The NICHD also supports research that is investigating the ways in which psychological processes such as memory, learning, attention, perception, and cognition are affected by individual differences in genetics, nutrition, and diseases. In addition, research pertaining to disorders of behavior and cognition associated with specific forms of learning disabilities, attention deficits, and hyperactivity is being supported.

In the coming year, efforts will focus on studies of the neural circuitry that underlies perception and cognition. This work will lay the ground work for understanding learning disabilities.

### *Injury Prevention*

Annually, 19 million children 15 years old or under receive medical care for an injury. A study estimated that in the toddler age group, one child in ten was treated in a hospital emergency room for injuries or poisonings. Epidemiologists have also estimated that injuries incapacitate two million children annually for 2 weeks or longer. Further, at least 100,000 children each year suffer permanent disability as a result of injuries.

Once infancy is past, injuries, not disease, become the leading cause of death and disability. In this field, prevention is of paramount importance. Preventive approaches involve both pediatrics and the behavioral sciences. For example, studies the NICHD has supported have developed and demonstrated the effectiveness of pediatric office-based interventions to have parents use car seats and seat belts for their children, and lower their home hot water heater settings to prevent scalding. To expand this research, the Institute last year issued a special solicitation for research grant applications on behavioral approaches

to injury prevention that invited scientists to submit proposals seeking to clarify the behavioral and environmental variables responsible for specific kinds of childhood injuries; to identify and measure observable behaviors of parents and children that are precursors of injury occurrence or injury avoidance (i.e., behaviors closely linked to injury morbidity and mortality); and to identify environmental conditions modifiable by parents or children that lead to injury or injury reduction. The solicitation also addressed the need for development of experimental models that explain, by use of analogy, the origins and continuation of risk-taking and safety behaviors, with a view toward developing effective intervention strategies.

One application which will be funded from this solicitation deals with increasing our understanding of how human behavior contributes to and can be modified to prevent injuries. The investigator's preliminary studies show that home hazards are influenced by developmental and environmental factors that can be objectively measured and experimentally analyzed, and that behaviors of children at risk for injury can be readily modified using learning-based procedures.

One consequence of the review of applications submitted in response to the Institute's solicitation was recognition of the need for improved knowledge of the kinds of methodologies required for sophisticated research on childhood injuries and their prevention. To accomplish this objective, the NICHD, in conjunction with the American Academy of Pediatrics, the American Psychological Association, and the Society for Research in Child Development, is organizing a research workshop on this topic, and will make the results available to investigators in this field to assist them in planning and designing future studies of childhood injury prevention.

The Institute is also soliciting, on a continuing basis under the Small Business Innovation Research (SBIR) program, proposals to develop procedures and devices that will reduce childhood injury and promote safety

in the home and environment. Furthermore, the Institute has recently recruited a pediatrician to direct and expand the Institute's research program in behavioral pediatrics.

### **Research Opportunities in Childhood Nutrition**

#### *Breastfeeding*

For more than 5 years the NICHD has encouraged coordinated grant and contract research on the nutritional and health benefits of human milk for the young infant. As a result of this research it is now clear that human milk is composed of a large array of constituents, many of them nutrients but others having important nonnutritive functions. For example, human milk appears to contain mechanisms to limit the digestion of its components until they reach the proper site for utilization. The research on breast feeding and the increased attention it has brought to the value of breast milk has led to the identification of a number of research areas where opportunities exist to further advance our knowledge.

In the area of the neuroendocrinology of milk production and release, it has been found that oxytocin is carried in the bloodstream to the breast where it initiates milk let-down at the commencement of feeding. Scientists are striving to learn how the brain translates sensory input associated with feeding (such as the infant's smell, sound, touch, and nipple stimulation) and the intraductal pressure that builds up between feedings into the synthesis and release of the oxytocin. Scientists are also working to identify the bioactive sites of prolactin, a polypeptide hormone secreted by the anterior pituitary gland, which causes breast tissue to develop, differentiate, and produce milk.

In the complicated interdisciplinary areas of biological and behavioral sciences, the Institute is encouraging investigators to identify and study the factors motivating mothers to breast feed their infants on one hand and those factors contributing to unsuccessful breast feeding and early weaning on the other.

Related to these studies and to increasing concern over premature and low birth weight infants is the need for studies investigating the composition and relative health benefits of the breast milk of mothers who deliver premature infants, the factors contributing to stimulating a mother's interest in breast feeding her premature or very small infant and the support mechanisms necessary to encourage her to lactate and contribute her milk to the nutritional support of her hospitalized low birth weight infant.

The increased attention given to the study of breast feeding and the expanding awareness of the nutritional value of breast milk has stimulated the establishment of an increasing number of milk banks. This development has brought with it a need to determine the best ways to collect, preserve and distribute human milk in a safe manner while retaining its valuable antimicrobial and growth-promoting components.

#### *Obesity*

Obesity is a condition of energy imbalance resulting in excessive storage of body fat such that body weight exceeds 120 percent of ideal weight for age, sex, height, and frame. By this definition, between 25 and 45 percent of American adults are obese. The widespread and ever-increasing prevalence of obesity in this country has become a major public health problem. It is linked to diabetes mellitus, atherosclerotic cardiovascular disease, hypertension, and some kinds of cancer. Therefore, investigations of the cause, prevention, and cure of obesity remain high research priorities.

A crucial research issue concerns the antecedents of obesity in childhood. The ultimate goal is to identify those individuals at high risk of becoming obese later in life and to design various kinds of preventive programs to meet their needs. The Institute staff, working with the NIH Nutrition Coordinating Committee, has issued a Program Announcement calling for studies on the genetic and physiological factors that influence weight gain, including studies on the neurochemical signals that modulate feelings of hunger



satiety food intake, and energy balance. The Institute has also expressed interest in receiving research applications on behavioral and low-calorie dietary intervention strategies used to treat obesity in childhood and adolescence.

Ongoing research includes studies examining the relationship between infant feeding practices and serum cholesterol levels of children aged 4 to 11 to test the hypothesis that the high cholesterol content of breast milk sets up mechanisms that allow for effective cholesterol metabolism in later life. Other longitudinal studies are assessing adolescent changes in lipid profiles and the relationship of these changes to sex hormones and obesity in normal and high-risk adolescent males; gaining an understanding of the relationship of parents' weight, habits, and provision of support to their children's obesity and weight loss; and increasing our understanding of the body's metabolic responses to low-calorie dietary therapy.

### **Adolescent Childbearing**

Adolescent childbearing is recognized as a leading health and social problem in the United States. Current research focuses on various determinants and consequences of adolescent pregnancy and childbearing. Issues revolving around adolescent pregnancy include initiating sexual activity, initiating and continuing contraception, and resolving an unexpected premarital pregnancy. Among those who are sexually active, adequate contraception is the most important factor discriminating teens who do not become pregnant from those who do. A related finding is that, although knowledge of contraception is important, the ability to communicate with parents and partners and motivation to avoid pregnancy are also important factors in effective contraceptive use. Concern has been expressed about whether sex education (including contraceptive information) will lead to increased adolescent sexual activity, yet research findings indicate that young people who have had sex education are no more like-

ly to have had sexual intercourse than those who have not. Moreover, sexually active young women who have had sex education are less likely to get pregnant than their counterparts who have had no such instruction. Further, it appears that teens who are encouraged by their families to finish school and have jobs and who believe that early pregnancy impedes these goals, are less likely to become pregnant.

Research has addressed the causes of the large number of teenage pregnancies each year (approximately one million) and the inherent risks associated with such pregnancies to the health and welfare of mother and baby. Although contraception is widely available, many sexually active teenagers appear to delay its use, to use less effective methods, and to contracept less consistently than adults. It has been hypothesized that there are behavioral and attitudinal reasons for this delay. To find out more about the behavioral and social factors resulting in less consistent and effective contraceptive use among teens, more emphasis was placed on research on these factors this year. The results of this emphasis on teen contraceptive behavior should start to appear in FY 1987.

### **Overcoming Infertility**

This priority of the Institute concerns a major health problem of the Nation—one out of seven couples desiring to have children are unable to do so. It addresses the alleviation of human infertility and the amelioration or cure of diseases and disorders affecting human reproduction. Among the studies within this area are those concerned with better delineation and understanding of reproductive processes in the normal (or fertile) person. Studies on male reproduction include those on varicocele, environmental effects on sperm production, genetic factors in abnormal sperm production, the contribution of male factors to habitual abortion, local events affecting sperm (such as circulatory change and local endocrine factors), autoimmunity, and endocrine and neuroendocrine disorders. Studies of factors affecting fertility in women include those on the cervix, the

uterine environment, tubal factors (local environmental factors, infection, surgical adhesions), studies of the ovary, and postcontraceptive infertility. Improved diagnostic and therapeutic techniques also are needed for both partners.

Recent findings in this area include a study that was conducted to evaluate the use of a new immunoradiometric assay (IRMA) for human chorionic gonadotropin (hCG) to discriminate between successful and failed pregnancies at short postconception intervals. It was found that the IRMA detected hCG at 100 times lower concentration than a comparison radioimmunoassay and was able to detect clinical pregnancies an average of 4 days sooner. The enhanced sensitivity and specificity of the IRMA detects the occurrence and loss of very early pregnancies that would otherwise be undetectable.

In response to stimulation by progesterone, uterine cells produce and secrete products necessary for the biological functions of the uterus. There is interest in detecting and characterizing specific hormone-dependent uterine proteins which may play vital roles in pregnancy. Recent studies in women have revealed that the glandular lining of the uterus (endometrium) contains a protein whose synthesis is significantly increased during early pregnancy. There is an apparent direct relationship in cycling of pregnant women between their endometrial concentration of this protein and their serum levels of progesterone. This protein has been called PEP for progesterone-associated endometrial protein. An immunological assay has been developed to quantitate the level of PEP in human endometrial tissues, amniotic fluids, and sera. The results have shown that normally cycling women have a characteristic pattern of PEP levels during their cycles which differs from that observed during pregnancy and abnormal cycles. Of particular clinical importance is the potential of this new marker for evaluating the presence, extent, and therapeutic response of women with luteal



phase defects, i.e., infertility therapy monitoring. In addition, PEP may be a sensitive and useful marker of pregnancy.

The adverse effect of smoking on reproduction is clearest in studies that demonstrate effects on the babies born to smoking as compared to nonsmoking pregnant women. Studies are aimed at evaluating the effects of smoking on male reproductive processes and, although the results are not yet completed, some interesting observations have emerged. A study of 30 infertile males suggests that smoking may influence sperm quality. Smokers showed more adverse variation in seminal fluid indices than did nonsmokers. The incidence of varicosities of the spermatic veins (varicocele) was higher in smokers as well. Studies are under way to ascertain the possible impact of smoking on the impairment of normal ovulation in women.

In the future, the objectives of this priority area are to support research on (1) the treatment of infertility in men and women; (2) the alleviation of human reproductive disorders; (3) the monitoring and prevention of ectopic implantation of embryos and pregnancy wastage; and (4) the relationship of pelvic inflammatory disease to reproductive failure.

## Policy Issues

A number of policy issues, substantive and structural, are of concern to the Institute; a brief description of their importance follows.

### Fetal Research

The Health Research Extension Act of 1985 essentially codified the fetal research provisions of the current DHHS Regulations (45 CFR 46), imposed a 3-year moratorium on the waiver provision of the regulations which is required for fetal research of greater than minimal risk, and required a study of the waiver provision by a Congressional Biomedical Ethics Advisory Committee. The 3-year moratorium extends a *de facto* moratorium which has been in existence since 1980. Thus, research of greater than minimal risk that may hold the promise for improving the survivability of fetuses and infants

(such as in *utero* treatments) will not be conducted or supported by the Federal Government for a 9-year period.

### Alternative Means of Reproduction

DHHS regulations for the protection of human subjects (45 CFR 46) require that a Departmental Ethics Advisory Board (EAB) review and approve all applications for human *in vitro* fertilization (IVF) research, and, by implication, research on all other alternative means of reproduction. The Department has not had an EAB since 1980. Concerned about its responsibility for the review of human IVF research applications, the NICHD Advisory Council at its September 1984 meeting petitioned the Secretary to reestablish an EAB so that pending human IVF applications could be reviewed. To date, an EAB has not been established and, although alternative means of reproduction are increasingly used in this and other countries, research which might clarify medical, ethical, legal, and other issues is not being conducted or supported by the Federal Government.

### Liability Insurance

Liability of potential Government contractors involved in the development of new means of fertility regulation to obtain liability insurance poses a potentially insuperable barrier to this research. The DHHS chooses not to use an indemnification clause (where the Government acts as a self-insurer). Pending the implementation of state and Federal legislative efforts to ameliorate problems in the liability insurance industry generally, contracts for projects that involve any risk to research patients will be difficult, if not impossible, to award. At this time four contract awards are being delayed.

### AIDS

AIDS relates to NICHD programs in the areas of reproduction and maternal and child health. Institute staff have developed proposals for research on: (1) the role of barrier

contraception in the prevention of AIDS transmission; (2) serial changes in HTLV-III and HTLV-I seroprevalence in a high-risk female population; (3) effect of HTLV-III infection on pregnancy; (4) clinical spectrum of HTLV-III disease in infants and children. These will be supported in FY 1986 from the NIH Office of the Director appropriation for AIDS research.

### Orphan Products

Institute research activities in rare diseases and orphan products are extensive. A few significant examples include:

- The use of human surfactant to treat Respiratory Distress Syndrome (RDS) in infants.
- The use of the antiglucocorticoid steroid RU-38486 to treat Cushing's Syndrome.
- The use of cysteamine, phosphocysteamine and pantetheine to treat cystinosis.
- The use of various reproductive hormones to treat a variety of problems such as precocious puberty and infertility.

### Infant Formula Study

The Infant Formula Act of 1980 directed the Secretary of DHHS to conduct a study to determine the long-term effect on infants of hypochloremic metabolic alkalosis resulting from infant formulas deficient in chloride. Following complications in initiating the study, the Institute awarded a contract in June 1984. The study is projected to be concluded in 1987, at which time a report will be forwarded to the Congress.

### NICHD Intramural Research Building

A research building to house the NICHD Intramural Research Program (now scattered in many different locations) will promote scientific interchange and productivity, increase the effective utilization of resources, and prevent complications arising from the movement of tissue culture and animals between laboratory buildings. Beginning in the 1960's, and continuing to the present, a consolidated location for all

NICHD laboratories has been planned. Original plans for the building have been updated and building concepts have been revised to take into account the latest in laboratory design principles and the most current programmatic thinking. Plans are to construct a building with significant emphasis on the neurosciences in a location that will promote cooperation with other Institutes in the sharing of primate and other facilities.

## **The Biennial Report of the Director, National Eye Institute**

### **History**

The following events represent milestones in the development of the National Eye Institute (NEI).

- August 16, 1968—Public Law 90-489 authorized the formation of the National Eye Institute.
- December 26, 1968—The National Eye Institute was established.
- April 3, 1969—The National Advisory Eye Council held its first meeting.
- 1970—Dr. Carl Kupfer was named Director of the Institute.
- December 15, 1970—Reorganization of the NEI resulted in the formation of an Office of Biometry and Epidemiology; an Office of the Director of Intramural Research; and a Laboratory of Vision Research and a Clinical Branch as the foci of intramural research.
- April 1975—Publication of the National Advisory Eye Council's report, *Vision Research Program Planning*, was the first comprehensive assessment of major needs and opportunities in vision research in the United States.
- April 1978—Publication of the National Advisory Eye Council's 5-year plan, *Vision Research: 1978-82*, included review and analysis of vision research and research training in the United States and discussion of future priorities.
- November 9, 1978—Public Law 95-623, Health Services Research, Health Statistics, and Health Care Technology Act, authorized the Secretary, DHEW, to carry out a program of grants for construction or renovation of public and nonprofit private vision research facilities.
- June 1981—A Laboratory of Molecular and Developmental Biology was established within the intramural research program.
- May 1983—Publication of the National Eye Council's second 5-year plan, a detailed and comprehensive assessment of NEI programs with recommendations for development over the next 5 years.

### **Introduction**

The NEI conducts, fosters, and supports basic and applied research related to the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system as well as investigations in related fields, including visual impairment and its rehabilitation, through:

- Research performed in its intramural laboratories and clinic.
- A program of research grants, individual and institutional research training awards, career development awards, core grants, and contracts to public and private research institutions and organizations.
- A program of grants for public and private nonprofit vision research facilities.
- Cooperation and collaboration with professional, commercial, voluntary, and philanthropic organizations concerned with vision research and training, disease prevention and health promotion, and the special health problems of the visually impaired and disabled and the blind.
- The collection and dissemination of information on ongoing research and findings in these areas.
- Cooperation and collaboration with domestic and international organizations in programs and projects for the worldwide prevention of blindness.

### **Implementation of Mission Through Program Planning**

The legislation establishing the NEI authorizes the NEI "to plan for research and training especially against the main causes of blindness and visual function." Indeed, the NEI believes that formal program planning is essential to carrying out its mission in the most effective and efficient manner. One of the stated rationales underlying NEI's planning process is "to encourage the highest possible rate of discovery and advancement in the sciences related to vision," a concept first articulated, interestingly enough, by a prominent neurophysiologist who was a member of the National Advisory

Eye Council at the time. Although it is not possible to prove that the recent research progress highlighted in the body of this report was hastened by program planning, the NEI is convinced that planning nonetheless fulfills a vital management function in providing a sound foundation on which to prepare budgets, formulate policies, and foster program development in areas of greatest need and opportunity. Because the NEI believes so strongly in its planning process and has based so much of its day-to-day and long-range management strategy on it, it seems appropriate to begin this first Biennial Report with a brief history and description of that process.

### Background

In 1973 the National Advisory Eye Council upon the suggestion of the NEI Director decided to initiate a formal planning process by asking a few leaders in the various scientific disciplines related to ophthalmology and vision research to survey their fields of expertise and to summarize broadly the state-of-knowledge, to identify areas that warranted more exploration and elucidation, and to outline a few of the most important research needs and opportunities over the succeeding 5 years. The result of their efforts was published in "Vision Research Program Planning," a two-volume set covering the years 1976-79, which was followed by a series of program plans published by the Council, each building and expanding upon what had preceded.

The most recent of these, "Vision Research—A National Plan: 1983-1987," is the most comprehensive and detailed of them all. It consists of nine books—including one for each of the five NEI programs—which together present an indepth assessment of the current NEI program as well as numerous specific recommendations for program development over the succeeding 5 years. In this effort more than 350 scientists, representing all major areas of vision research, helped refine and improve the NEI program planning system and provided scientific guidance on the setting of research priorities.

For each NEI program, this plan describes significant diseases and disorders, including their public health impact and the research disciplines that the program addresses; defines program goals and objectives; surveys current support by the NEI and other organizations; reviews recent program and research accomplishments; describes current relevant research needs, opportunities, and approaches; and makes specific recommendations concerning program development.

This report defines several program priorities and projects of resource requirements for each major area of vision research that the NEI supports. In addition, this plan discusses how the vision research projects the NEI supports relate to the following cross-cutting health science areas and issues, several of which are the subject of considerable national interest for scientific, economic, social, or political reasons: disease prevention, diabetes, nutrition, aging, toxicology, genetics, immunology, epidemiology, neurobiology, molecular biology, noninvasive research and diagnostic techniques, refractive errors, and the use of animals in vision research.

In the summer of 1986, the Council published an evaluation of the 1983 plan, including a discussion of significant recent accomplishments, the status of ongoing research activities in terms of how well they have fulfilled the plan's recommendations, and revised priorities for the next 2 years.

### Planning Principles

Over the course of its planning endeavors, the Council has developed several general planning principles during its initial planning activities in 1975, which still guide the process today. Among the most important of these are:

- The NIH investigator-initiated research project grant (ROI) must be relied on as the primary mechanism of NEI research support. Indeed, in FY 1985, ROIs accounted for 88.4 percent of NEI's extramural budget.
- The program planning process must be prospective and continuous and its outcome should be communicated rapidly to the scientific

community and the general public. In fact, successful implementation of NEI program plans depends heavily on wide dissemination and knowledge of the contents of these plans.

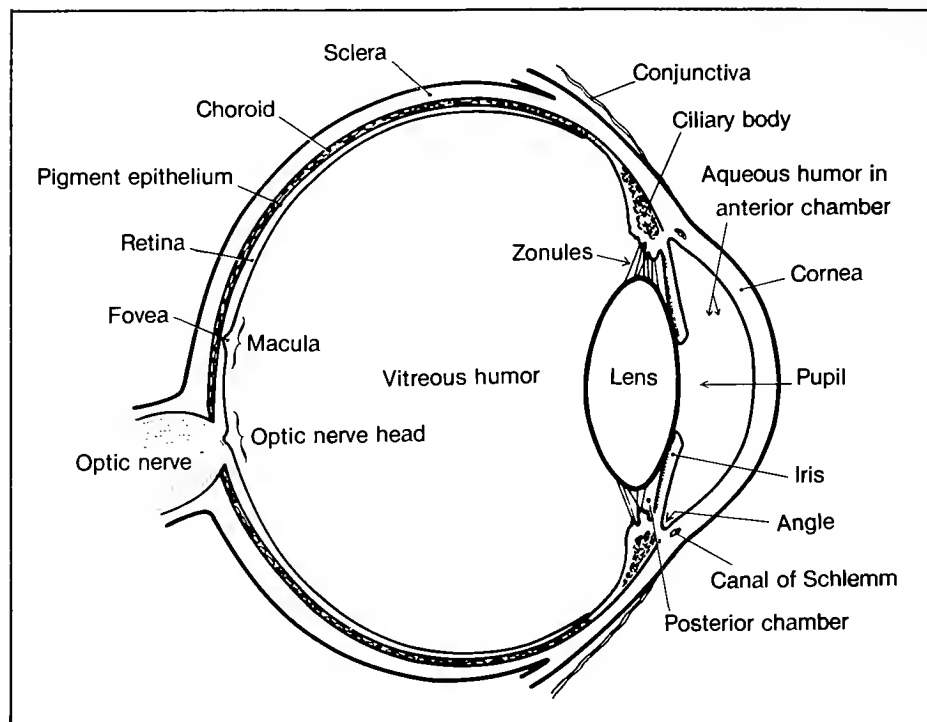
### Implementation Guidelines

In addition, the NEI abides by the following guidelines, also developed early in the NEI planning process, in implementing its national plans:

- Continue to fund first all proposals for research projects that are judged to be of the highest scientific quality by NIH study sections and other initial NIH peer review groups.
- Emphasize research that is judged the most relevant to the prevention, diagnosis, and treatment of blinding and visually disabling disorders.
- Stress basic biological and applied clinical research on problems related to the most common causes of blindness and visual disability.
- When research involves laboratory animals, favor the utilization of species for which both scientific opportunity and technical feasibility permit the greatest amount of generalization to the human condition.

### Scientific Opportunities and Research Advances

All vision research conducted and supported by the NEI is classified into five major programs that encompass a full spectrum of basic and applied research on a large number of eye and visual disorders that are the most important causes of visual deprivation and blindness in the United States. The five programs are: Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing. Because of the importance of the broad topic of irreversible visual impairment and its rehabilitation, special consideration has been given in the national plans to this subject, which has relevance to most of the diseases covered in the five NEI programs. Each of the five programs is further divided into subprograms,



*Schematic cross section of the human eye showing major components.*

which generally focus on specific ocular and visual system diseases or disease processes, normal ocular functions, tissues, or systems.

Among the five programs, there are naturally many areas of mutual and even overlapping concerns. For example, the ocular effects of diabetes are of interest in both the Retinal and Choroidal Diseases Program and the Cataract Program. Congenital and developmental eye disorders are common to all five programs. Because of these shared problems and concerns, progress in one area of vision research may well lead to advances in another. This indicates the need for improved communication among scientists in the various specialized fields of vision research and for their increased collaboration in investigations of mutual interest.

The following sections present a short introduction to each of the five NEI programs, summarize major research and program progress during FY 1985-86, highlight the current status of noteworthy NEI-supported investigations, and indicate future research needs and priorities.

### **Retinal and Choroidal Diseases**

The retina is the delicate, multi-layered, light-sensitive membrane that lines the inside of the back of the eye. The normal functioning and survival of the thousands of light-sensitive and other neural cells that the retina comprises depend on a carefully controlled environment and a continuous supply of oxygen and nutrients supplied by two systems of blood vessels, one within the retina and the other in the highly vascular choroid, the tissue lying immediately underneath. Damage to the retina, interruption in its blood supply, or injury to the tissues with which it interacts, such as the pigment epithelium (a single cell layer between the retina and choroid that controls many nutritive exchanges between the blood and the retina) can lead to loss or severe impairment of vision. Unfortunately, the retina is susceptible to injury in numerous ways, including damage from systemic disorders such as diabetes and sickle cell anemia, infection and inflammation, circulatory failure, hereditary factors, aging, trauma, and toxic and environmental factors.

These disorders, which as a group are the leading cause of blindness in

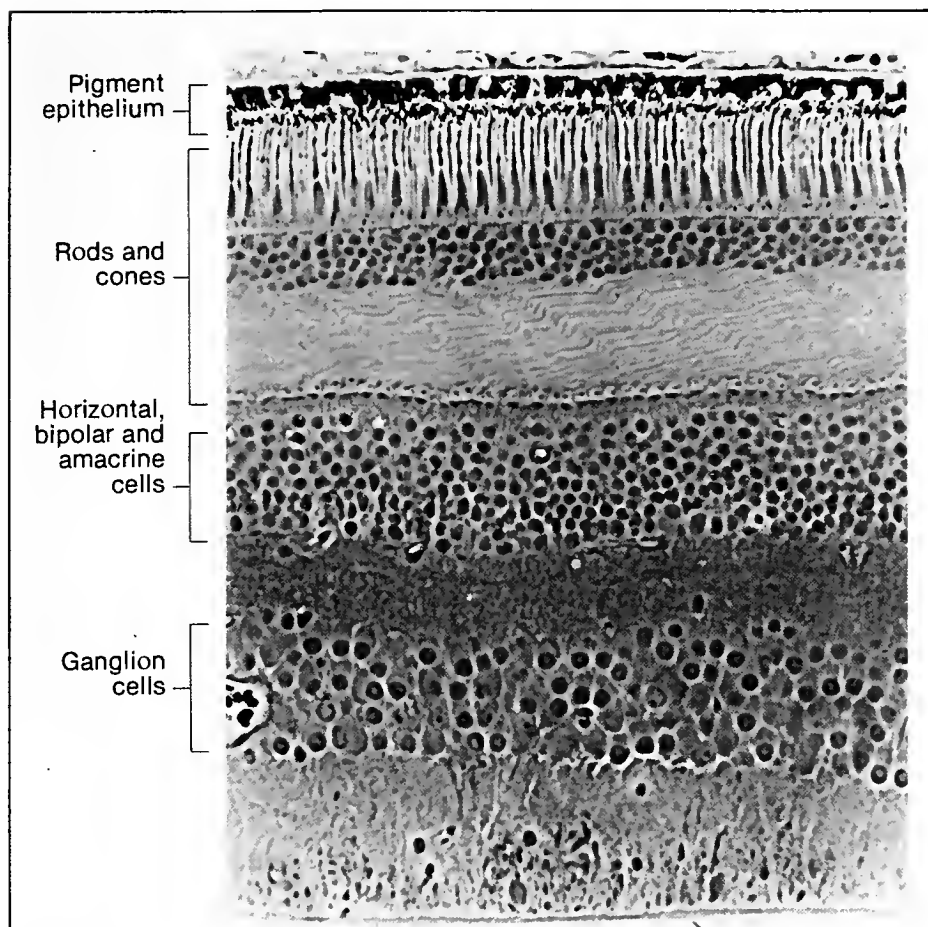
the United States, cause approximately 200,000 cases of legal blindness in this country. Each year 19,000 additional Americans become blind from retinal and choroidal diseases. One of these diseases, diabetic retinopathy, is the leading cause of new cases of blindness in adults under age 65, and another, aging-related maculopathy, is the leading cause of new cases of blindness in people age 65 and older.

### **Diabetic Retinopathy**

Diabetes affects a number of eye tissues, but exerts its most harmful effects on the tiny blood vessels of the retina where it triggers a series of events that may lead to severe and irreversible vision loss. Timely laser treatment can halt the progress of advanced diabetic retinopathy and forestall blindness in a large percentage of cases. In some instances, when blood leaks into the vitreous humor and is not resolved, the resulting impaired vision can be improved through a surgical procedure known as vitrectomy. Although these advances have benefited thousands of people, the search continues for better methods to treat and prevent or cure diabetic retinopathy.

In an NEI-supported clinical trial, the Early Treatment Diabetic Retinopathy Study (ETDRS), focal photocoagulation, a type of laser treatment, is being evaluated in patients who are still in the early stages of diabetic eye disease. Recent results from this study show that it is possible to halt or even reverse the vision loss that occurs in many people with diabetic macular edema—swelling in the small portion of the retina that provides sharp, central vision.

The Diabetic Retinopathy Vitrectomy Study (DRVS) is a clinical trial comparing early vitrectomy with deferred vitrectomy in individuals with diabetic retinopathy who have recently suffered a severe vitreous hemorrhage. Vitrectomy is a surgical procedure for removing the blood that leaks from abnormal retinal vessels into the clear jelly-like material (the vitreous) inside the eye. This leakage of blood may induce scar tissue formation that can



*Section through a human retina, showing the principal cell types and layers. Light passes through the entire retina before reaching the outer segments of the photoreceptors, where it is absorbed by the visual pigments and converted into electrochemical signals. Complex processes modify the signals as they are conveyed to the photoreceptors, synaptic terminals where the visual message is transmitted to adjacent bipolar and horizontal cells for further processing. Additional information processing occurs by means of the complex synaptic interactions of the various retinal cells with one another. The results of this processing appear ultimately in the message carried by the ganglion cell axons (the optic nerve) to the brain.*



*Studies supported by the National Eye Institute have demonstrated that treatment with a laser dramatically reduces the risk of visual impairment from the ocular complications of diabetes, neovascular type of senile macular degeneration, and ocular histoplasmosis syndrome. Diabetic retinopathy and neovascular senile macular degeneration are two of the leading causes of blindness among adults in the United States. Laser treatment is also being widely used in the treatment of various kinds of glaucoma. (Left)*

cause retinal detachment and ultimately lead to permanent vision loss or blindness. Investigators have found at 2-year followup examinations in the DRVS that a higher percentage of eyes undergoing early vitrectomy recovered a 20/40 visual acuity than did the eyes in which the treatment was deferred in hope that the hemorrhage would clear on its own. The percentage recovering 20/40 vision was even higher in type I (juvenile onset) diabetics. The investigators have concluded that early vitrectomy can improve chances of long-term recovery of good vision in some eyes.

In diabetic retinopathy the uncontrolled growth of retinal vessels (neovascularization) may be due to the presence of growth (angiogenic) factors at the cellular level. A recent discovery that vascular endothelial growth factors bind to heparin, a compound often used as an anticoagulant, is an important breakthrough because it will allow scientists to purify these growth factors by binding them to heparin. Until the development of this methodology it had been difficult to purify angiogenic factors; but, now that this can be done quite easily, rapid progress in gaining an understanding of the neovascular process can be expected.

Because an adequate supply of oxygen to the retina is crucial to the maintenance of visual function, a study is being conducted to measure intraretinal oxygen tension with microelectrodes. It is hoped that this will allow the development of a mathematical model of retinal oxygenation, which may improve understanding of its role in the neovascularization that occurs in diabetes.

The Sorbinil Retinopathy Trial is the latest in a series of NEI-fostered clinical trials to evaluate various means of preventing and treating the harmful effects of diabetes on the eye. The NEI and Pfizer, Inc., the drug's developer, are collaborating on a study to determine if the eye problems and nerve damage that may occur as a result of diabetes can be prevented or their development slowed. Physicians at



the participating centers will administer a new, investigational aldose reductase inhibitor, called sorbinil, in the hope that this drug will protect the sight of people who do not yet have signs of eye problems, specifically retinopathy. NEI investigators have identified aldose reductase as an enzyme that may play a key role in the damage caused by diabetes throughout the body. Their laboratory findings suggest that inhibitors of aldose reductase, such as sorbinil, might prevent eye and nerve complications of diabetes. The study will include 11 eye care centers across the United States, each of which will enroll more than 50 patients to evaluate sorbinil's effectiveness in preventing or slowing the progression of diabetes-associated retinopathy and nerve damage.

The laser Doppler technique is a noninvasive means of measuring blood flow rate, which may be impaired in diabetes, at selected sites in the retina. It is being used to characterize quantitatively the retinal circulation of selected patients with diabetic retinopathy, to aid in diagnosis, to determine prognosis, and to monitor the effectiveness of therapy.

Continued support for clinical trials of treatments for retinal vascular diseases and for testing the efficacy of rigorous blood sugar control in the prevention of diabetic retinopathy remains a research priority for the Institute. Future investigations in this area will be aimed at isolating and characterizing substances that lead to or inhibit uncontrolled blood vessel growth in the retina.

#### *Macular Diseases*

Disease that selectively affects the macula, the small area of the retina that provides sharp central vision, occurs primarily with aging, impairing to some degree the vision of millions of Americans over age 50. When this disease becomes severe it is capable of depriving the elderly of their ability to read and may even limit mobility. In fact, aging-related maculopathy is the leading cause of severe vision loss among people age 65 and older. The impact of diseases affecting the macula will increase in

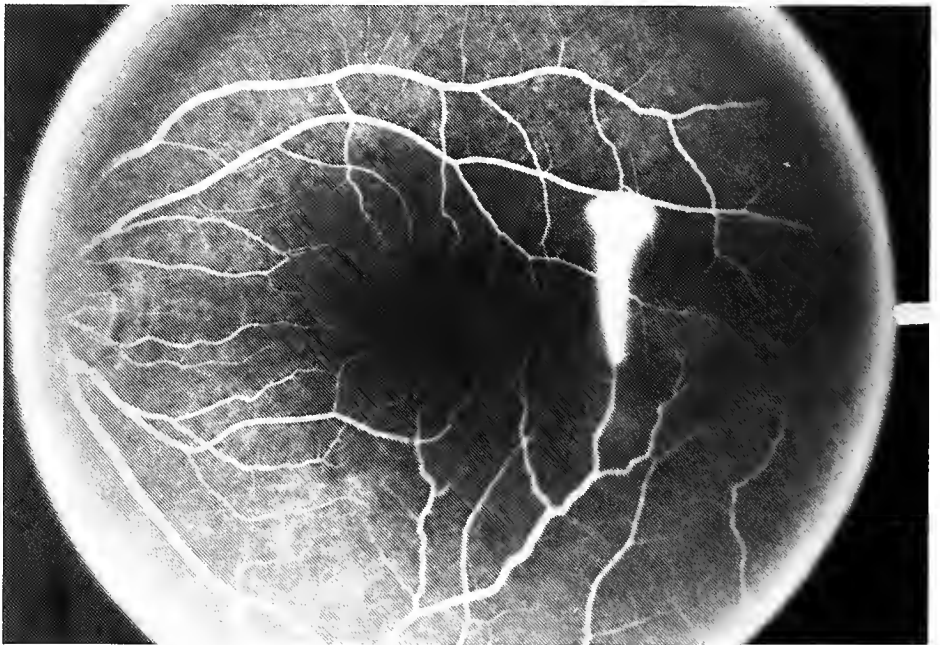
the future as the number of aged people in our population increases. Major clinical studies have been and are being conducted to investigate treatments for types of macular disorders.

In May 1982, a nationwide clinical trial sponsored by the NEI, the Macular Photocoagulation Study (MPS), provided the first conclusive evidence that laser treatment, if carried out within days or weeks after onset of symptoms, can be highly effective in preventing severe vision loss from the neovascular type of aging-related maculopathy, which is characterized by the formation of abnormal new blood vessels between the retina and choroid near the macula. Most legal blindness from aging-related maculopathy is due to this neovascular form, which affects approximately 116,000 people in the United States. Evidence from this study suggests that the vast majority of such cases of blindness could be prevented or delayed significantly by timely laser treatment if the disease is recognized early. Although these findings are impressive, much more research is needed to find better ways of treating and ultimately preventing aging-related maculopathy.

The MPS has also reported the results of the Ocular Histoplasmosis Study, the purpose of which was to determine whether laser photocoagulation would be of any benefit in preventing loss of visual acuity in eyes with evidence of ocular histoplasmosis and associated abnormal growth of new blood vessels. Histoplasmosis is a fungal infection which has ocular involvement in about 4 percent of the people in the United States who react positively to the skin test for the disease. The results of the most recent followup visit (median 18 months) showed that 34.2 percent of untreated eyes compared with 9.4 percent of treated eyes lost significant visual acuity. Although recruitment for this study was terminated because more untreated eyes than treated eyes had experienced severe visual acuity loss, followup of patients continues to assess long-term treatment results.

#### *Hereditary and Developmental Disorders*

Much attention is directed to inherited retinal diseases, such as retinitis pigmentosa, a disorder that most often strikes young people during their critical learning years. This disease, for which there is no



*Leakage of fluorescein during angiography in smokestack configuration in a patient with central serous choroidopathy, a condition characterized by separation of the sensory retina from the pigment epithelium in the central retinal area by a serous fluid.*



known cure or means of prevention, causes night blindness and a gradual restriction of the visual field. Those affected face a lifetime of vision impairment and disability.

Two NEI grants have contributed significantly to recent advances in locating the genes responsible for hereditary retinal degenerations. These studies have confirmed and refined other investigators' estimates of the location of the gene for one form of retinitis pigmentosa. In addition, the gene for an enzyme that has been shown to be deficient in patients with gyrate atrophy, a blinding deterioration of the retina of the eye that begins in childhood and is related to retinitis pigmentosa, has been isolated by NEI-supported researchers. This will not only help scientists better understand the molecular basis of this disease but may also provide useful information for genetic counseling and increase the potential for development of gene therapy for this and related blinding diseases.

The effects of intense light exposure in normal rats and a strain with inherited retinal dystrophy are being determined by measuring light-induced changes in proteins and lipids within the retina. Prolonged exposure to high intensity light has been shown to produce photoreceptor damage, whereas rearing retinal dystrophic rats in the dark has been shown to decrease the rate of retinal degeneration. These studies may lead to a better understanding of hereditary retinal degenerative conditions such as retinitis pigmentosa and may ultimately allow the development of measures to prevent or retard the degenerative process and, in so doing, spare many people from the lifelong burden of visual handicaps acquired in childhood.

In the past year the NEI has inaugurated a major clinical trial to evaluate cryotherapy as a method of halting the progression of a blinding disease of low-birth-weight infants (called retinopathy of prematurity) in severely affected children. In this procedure selected sites on the sclera (the white of the eye) are frozen with a cryoprobe, thereby altering the underlying retinal tissue



*Recurrent human herpes simplex infection of the cornea with multiple large dendritic ulcers.*

and creating a barrier that prevents the abnormal growth of tissue and blood vessels that threatens to detach the retina in the earlier stages of this disease.

#### *Inflammatory Diseases*

Inflammatory disorders of the retina and choroid comprise a large group of destructive—often painful—diseases, referred to collectively as uveitis. These diseases often affect not only the retina and choroid but also the vitreous body (the transparent gel that fills the center of the eye) and the front of the uvea (the ciliary body and iris).

The S-antigen, a molecular component of the retina photoreceptor cell, has recently been cloned and sufficiently purified to demonstrate its ability to trigger some forms of uveitis. This finding suggests that these disorders are autoimmune in nature; that is, they are triggered when the eye generates an inflammatory response to its own tissue components as if they were foreign invaders.

Characterization and localization of other antigens of specific retinal cell types—Muller and horizontal cells—are being attempted with monoclonal antibodies. These studies should

yield information needed to determine the possible relation between these antigens as well to autoimmune diseases of the eye.

Future research in this area will emphasize developing and improving methods for the definition and diagnosis of ocular inflammatory disease and for further determination of the role of the immune system in other ocular disorders. Also, application of recombinant DNA technology to explore gene expression and basic mechanisms in ocular inflammatory disorders will be a research priority.

#### **Corneal Diseases**

The cornea is the transparent tissue at the front of the eye that plays a key role in refracting or bending light to focus images sharply on the retina. Because the cornea is the most exposed surface of the eye, it is particularly vulnerable to damage from injury, infection, toxic agents, and environmental pollutants.

Corneal diseases and injuries account for only about 6 percent of all legal blindness in the United States, but such disorders are the primary cause of blindness worldwide, due to infections and vitamin A deficiency. In addition, they are generally the most painful of all ocular

disorders and account for considerable visual disability. In the United States approximately 62 percent of all annual cases of eye diseases affect the cornea. They account for more than 100,000 hospital days and more than 8 million office visits annually for professional eye care. Eye injuries, which primarily affect the cornea, account for an additional 1.7 million annual visits to physicians.

#### *Viral Infections*

Herpes simplex virus (HSV) is the leading infectious cause of corneal blindness and vision impairment in the United States. Acute ocular herpes infections are difficult to treat, but a number of effective antiviral drugs are now available. In fact, most of the antiherpes drugs now on the market were first tested and proved effective in the eye, and research on ocular herpes and its treatment has made a major contribution to knowledge and treatment of herpes infections generally. Unfortunately, none of the present agents can prevent recurrences of ocular herpes due to reactivation of latent virus residing within nerve tissues behind the eye. Thus, further research on this painful and disabling condition is of high priority.

Although an initial HSV infection may subside after treatment, nearly 25 percent of those infected experience a recurrence of the epithelial disease or a complication of the infection in the stromal layer of the cornea within 2 years of the initial infection. Vision scientists have developed an *in vivo* experimental system for reactivating latent (HSV) infection from neural tissue, making it possible to study this process.

An improved method for delivery of antiviral drugs to the site of HSV infection is also being evaluated. Liposomes (minute lipid-bound sacks) containing a variety of antiviral drugs which have specific antibody against HSV on the surface are being constructed. These immunoliposomes should attach specifically to virus-infected cells and allow the drug to diffuse from the liposome, creating a high local concentration of the drug for a prolonged period. This should inhibit viral replication close to the attachment site and

reduce the frequency of topical administration required for effective treatment.

Scientists have developed better reagents (monoclonal and polyclonal antibodies) and more elegant techniques to identify adenoviruses isolated from the ocular surface and from cell cultures. These technical advances have improved the rapidity and sensitivity of the detection of these viruses, which have been shown to cause a keratoconjunctivitis and cancer in laboratory animals.

Priorities for future research in viral infections of the cornea include the use of simian varicella virus as an animal model for human varicella-zoster infection of the eye and evaluation of new antiviral and anti-inflammatory agents for therapy of ocular infections due to adenoviruses and other viruses.

#### *Corneal Transplantation*

Corneal transplantation, one of the oldest and most successful of all tissue transplant procedures, has restored sight to many thousands of people who would otherwise have been permanently blinded by corneal injury or disease. Research supported in the NEI Corneal Diseases Program seeks to improve the already high success rate of corneal transplantation and extend its use to treating disorders which at present are not generally amenable to such therapy.

Of the small percentage of corneal grafts that do fail, immune rejection is the leading cause. Research is currently aimed at gaining an understanding of the rejection process and attempting to modify or eliminate it. Donated corneas that have been soaked in a solution containing antibody against the histocompatibility (human lymphocyte) antigens found on the surfaces of most tissues have been shown to have an increased survival rate when compared to unsoaked grafts.

A six-center clinical trial, the Cooperative Corneal Transplantation Study, includes patients requiring corneal transplants who are at high risk of transplant rejection (that is, they have highly vascularized corneas or a prior history of rejection).

Some of these patients will be given corneas whose human lymphocyte antigens (HLA) most closely match their own, while other patients will be given corneas whose HLAs do not match their own. This should allow determination of the effectiveness of HLA testing in preventing graft rejection in high-risk patients.

Studies are also being conducted on the transplantation of cellular material from tissue culture to damaged or diseased corneas. Tissue-cultured corneal endothelium and endothelium from the lining of blood vessels have been transplanted successfully in animals, resulting in a return of normal corneal endothelial physiological function, morphology, and clarity. Additional work still needs to be done before this procedure can be used in endothelial replacement and repair in humans.

Research on contact lenses and surgical methods of refractive error correction is also a vital element of this program. Future emphasis will include the study of the biological effects of synthetic corneal implants for the correction of refractive errors.

#### *Vitamin A Deficiency*

Scientists are investigating the observation that the surface of the eye seems to be more vulnerable to injury when there is nutritional vitamin A deficiency. Vitamin A deficient rabbits with corneal lesions similar to those found in children who are vitamin A deficient are being studied. In addition, clinical studies of such children in developing nations (where malnutrition is common) are now under way to define the mechanism responsible for the high incidence of blindness associated with measles and other infections.

#### *Tear Film*

Considerable attention has recently been focused on the tear film and its importance in maintaining the health of the cornea and ocular surface cells. Recognition of the extreme complexity of the tear film was one of the conclusions of the Tear Film Symposium which was recently sponsored by the NEI and brought together researchers from the United

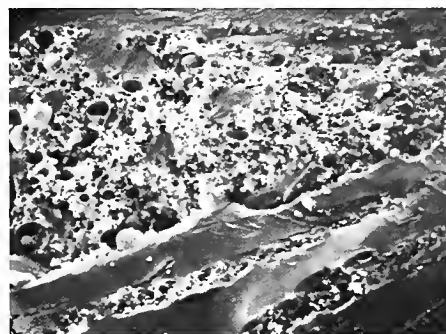
States and abroad to discuss the current status of tear film research and therapy. The outcome of these deliberations has been renewed research activity in tear film composition and function and increased focus on research techniques to improve understanding of ocular surface problems.

### Cataract

A cataract is an opacity of the eye's normally clear lens that interferes with vision. Although usually occurring in old age, cataract may develop at any time in life, beginning even before birth. It may be a consequence of diabetes or other metabolic disorders, trauma, or exposure to toxic agents and radiation, or cataract may be inherited or congenital in nature.

About 60 percent of people between the ages of 65 and 74 show some signs of cataract, and about 3.3 million people in the United States are visually impaired by this disorder. At least 43,000 people are blind from cataract, making it the third leading cause of legal blindness in the United States; about 4,700 new cases of blindness from cataract occur each year.

At present, surgery to remove the opaque lens is the only effective way of treating cataract. Techniques developed over the past 25 years have made cataract extraction one of the safest and most successful major operations. According to the United States Hospital Discharge Survey, an estimated 541,000 cataract extractions were performed in 1981 in the United States at a total cost of nearly \$1.4 billion. About 90 to 95 of these operations were successful in restoring useful vision when intraocular lens (IOL) implants, eyeglasses, or contact lenses were used. Nonetheless, because it is always desirable to avoid surgery if possible and because complications or unsatisfactory vision adjustments still occur following a small percentage of cataract extractions, the National Eye Institute devotes most of its funding in the Cataract Program to research aimed at developing means of preventing or slowing the development of cataract or of treating it nonsurgically. We have estimated that if it were possible to slow the progression of cataract enough to delay the need for surgery by only 10 years, the number of cataract operations



*Scanning electron micrograph of a human cataract showing globular alterations in the lens cortex (X225).*

performed in the United States could be reduced by 45 percent annually.

### Diabetic Cataract

The enzyme aldose reductase, normally present in several tissues of the body, has been increasingly implicated in the etiology of diabetic complications. A decade of basic research on the formation of diabetic cataracts through the action of aldose reductase has not only paved the way for the development of drugs such as sorbinil that inhibit the enzyme, but has also stimulated investigation into the role of aldose reductase in a variety of other diabetic complications. Ongoing work should lead to a more precise understanding and control of the pathological effects observed in diabetes and be useful in designing anti-cataract drugs.

Studies are ongoing in animals to evaluate the use of a variety of aldose reductase inhibitors in protecting against diabetic cataract development, arresting further cataract development, and promoting a reparative process. In addition to aldose reductase, the roles of other sugar metabolizing enzymes are being studied during the development of diabetic cataracts in higher animals and people having adult-onset diabetes.

### Molecular Genetic Research on Lens Structure and Function

Crystallins are the unique proteins responsible for the lens's transparency. Significant advances have been made in characterizing crystallin structures, and molecular studies on crystallin genes have been initiated.



*Early human cataract. This photograph of an extracted semi-opaque lens, which shows distortions of gradient lines placed behind the lens, is used to classify the density of the cataract.*

The cloning of crystallin genes in bacteria holds promise for further elucidation of the protein and genetic activity in the lens which is important in normal lens cell development and differentiation.

Recent experiments have also shown that a crystallin gene can be inserted into the chromosomes of mice, resulting in production of that crystallin in the lens of the mouse. This indicates that it is now theoretically possible to correct crystallin gene deficiencies that may be related to genetic cataracts.

Advances in molecular biology have also made it possible to study the alteration of lens proteins and investigate the extent to which such alteration affects transparency. Studies have indicated that oxidation of protein and lipid components of the lens is related to the onset of senile cataract. A prime factor leading to this oxidative damage appears to be the ambient ultraviolet light radiation in sunlight.

Dramatic progress has been made in developing nuclear magnetic resonance techniques to monitor changes in lens components noninvasively. These techniques offer the possibility of detecting changes in the lens well before the appearance of an opacity.

A priority for future research in this area is to develop lens cell culture systems to study cell division, gene transfer and expression, the effects of drugs on ocular tissues, and lens metabolism.

#### Other Studies

The effect of aging on the lens fiber membrane, protein synthesis, and the accumulation of water-insoluble protein in normal lenses is being studied. Studies of human senile cataract and selenium-induced cataract strongly suggest that toxic by-products of oxidative metabolism, such as hydrogen peroxide, hydroxyl ions, or singlet oxygen, are triggering agents in the development of cataract. Attempts are being made to prevent or arrest cataract in animal models by using antioxidants.

Various epidemiologic studies of cataract are under way to determine environmental, nutritional, and genetic factors that may be involved

in cataract development. During the past year, the NEI initiated a case/control study of senile cataract in India. Senile or aging-related cataract is a major cause of blindness and visual disability throughout the world. The aim of this study is to evaluate associations of risk factors, such as nutritional status and family history, with major types of senile cataract and to evaluate methods of cataract classification.

A number of researchers are using immunochemical and biochemical techniques to study lens components in normal and disease states. These studies include ultrastructural, biochemical, and immunological characterization of the zonules—the elastic fibers which support the lens. Investigations of the normal state of these fibers are expected to provide valuable information on the abnormal conditions which lead to lens dislocation as well as to presbyopia, the aging-related condition that requires middle-aged people to use reading glasses.

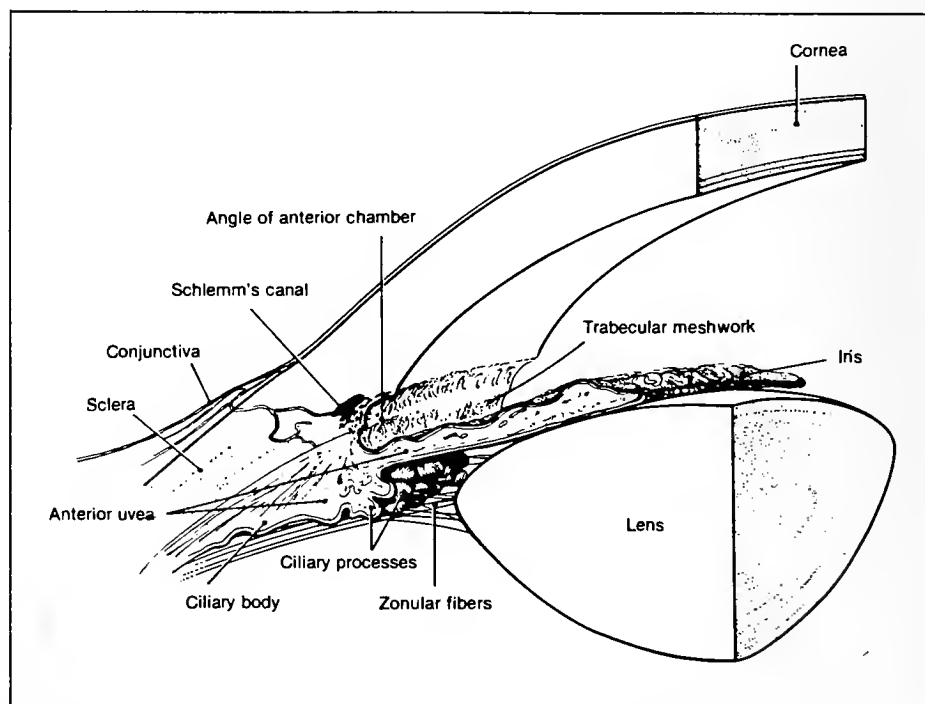
Investigations are in progress to increase understanding of the transport of inorganic ions and organic nutrients across cellular plasma

membranes in the lens. Since the lens is dependent on diffusion of nutrients from the aqueous humor, the fluid that circulates between the cornea and the lens, an understanding of this process may help to determine the clinical significance of deficiencies in transport that can develop during cataract formation.

#### Glaucoma

There are many types of glaucoma, most of which are characterized by an abnormally high level of the fluid pressure within the eye (intraocular pressure) accompanied by progressive destruction of peripheral vision due to irreversible damage to the optic nerve.

Although glaucoma may occur at any time in life, and there are severe congenital forms of the disease, the risk of developing glaucoma increases with age. Approximately 62,000 Americans are legally blind from glaucoma, and about 1.2 million Americans are known to have this disease. An equal number may be unaware that they have glaucoma. In addition, as many as 10 million people may have elevated intraocular pressure called "ocular



*Schematic section of the human eye showing structures discussed in the Glaucoma Program. The iris and ciliary body constitute the anterior portion of the uveal tract.*

hypertension," but show no optic nerve damage, although some will eventually develop glaucoma. Conversely, a significant number of people suffer optic nerve damage even though they have what is considered normal intraocular pressure. This condition is referred to as "low tension" glaucoma. At present, there is no sure way to predict which people, with or without ocular hypertension, are at risk for developing glaucoma or losing vision.

Normal intraocular pressure is maintained by balancing the continuous production of fluid within the eye and the rate of its drainage from the eye. This fluid, the aqueous humor, which is produced primarily by the ciliary body, passes between the iris and the lens and fills the anterior chamber, the space between the lens and cornea, thereby providing nourishment to these transparent tissues which have no blood supply. Fluid leaves the eye by filtering through the trabecular meshwork and the canal of Schlemm, the tissues located in the area enclosed by the angle formed by the juncture of the iris and the cornea. Almost always it is the blockage of the aqueous humor exit pathways, rather than overproduction of fluid, that is the cause of increased intraocular pressure in glaucoma.

Although glaucoma may be controlled, most forms of the disease cannot be cured. The predominant form of glaucoma, accounting for up to 80 percent of all cases of the disease, is known as primary open-angle glaucoma. In this condition and in ocular hypertension and low tension glaucoma, outflow of aqueous humor is impaired although no anatomic blockage is apparent in the filtration angle. One research approach to this problem is focused on the possibility that submicroscopic particles may clog the filtration channels.

#### *Epidemiology*

Epidemiologic studies are under way to determine the risk factors for open-angle glaucoma, especially to evaluate possible racial differences in these factors. In population studies, blood pressure and body weight have been found to be positively

correlated with intraocular pressure. Myopia has been demonstrated to be a risk factor for open-angle glaucoma. Epidemiologic evidence also suggests that migraine is also a risk factor. A better understanding of the risk factors for glaucoma, developed through the use of modern epidemiologic methods, could well improve the clinician's prognostic ability, shed light on disease mechanisms, and perhaps point the way to earlier and better treatments.

#### *Aqueous Humor Studies*

Understanding the physiology of the formation of aqueous humor has increased through the development of aqueous fluorophotometry, a method for measuring aqueous humor flow. Studies using this method have already provided important information about the physiologic mechanisms of drug actions (particularly in humans), basic physiologic data on the daily fluctuations in aqueous humor formation, and changes in aqueous humor formation in disease.

The use of cell culture methods has provided new opportunities to study trabecular cells, those which compose the trabecular meshwork in the front portion of the eye through which the aqueous humor flows out of the eye. Trabecular cells play a key role in the maintenance of normal outflow of aqueous humor from the anterior chamber, in alterations that may take place in different types of glaucoma, and in responses to drugs that influence aqueous humor outflow.

Exploitation of advances in transport physiology, immunocytochemistry, cell biology, and molecular biology to investigate local and intracellular mechanisms that govern aqueous humor formation and outflow is a priority for future research in this program.

#### *Studies of the Mechanisms of*

#### *Visual Function Loss in Glaucoma*

Glaucoma is diagnosed by measuring intraocular pressure, observing typical changes in appearance of the optic nerve head with an ophthalmoscope, and measuring changes in the field of vision. Because the

progress of glaucoma often can be stopped or at least slowed by drugs or surgery to reduce intraocular pressure, blindness can usually be prevented if the condition is detected and treated early. However, once vision is damaged or lost because of glaucoma, it cannot be restored.

The fact that glaucoma remains a major cause of blindness, despite the availability of various ways of controlling intraocular pressure, indicates the need to understand better the mechanisms by which increased intraocular pressure causes optic nerve damage and to develop more effective means of early detection, prevention, and treatment.

Studies using light and electron microscopic analyses of human tissues obtained following well-documented clinical disease have aided understanding of the mechanisms by which the optic nerve is injured in glaucoma. In addition, an attempt is being made to identify factors other than intraocular pressure that influence the susceptibility of an optic nerve to glaucomatous damage.

The pathogenic process by which elevated intraocular pressure causes the death of retinal ganglion cells is being investigated. The possible causes for the increased susceptibility to glaucoma found in aged, myopic, and black people are also being examined.

Priorities for future research in this program include development of new noninvasive methods for studying the pathophysiologic mechanisms of glaucomatous optic nerve damage in human eyes and the application of new techniques in immunocytochemistry and cell biology to study the optic nerve head in normal and glaucomatous eyes.

#### *Treatment*

Treatment for glaucoma, whether by drugs or surgery, is aimed either at diminishing aqueous humor production or at facilitating its outflow. In the search for a cure for glaucoma, an understanding of the normal cellular processes that regulate the flow of aqueous humor through the eye, how they are changed as the disease is initiated and progresses, and how drugs act upon them is



essential, as is determining how optic nerve damage is related to intraocular pressure. An understanding of the basic physiologic processes in the optic nerve that are affected in glaucoma should ultimately lead to the development of ways to protect the optic nerve and perhaps eventually to reverse nerve damage.

In an attempt to improve the outcome of glaucoma surgery, the compound 5-fluorouracil, a chemical that inhibits cell proliferation, is being administered postoperatively under the conjunctiva of the eye in a randomized clinical trial. Administration of this chemical has been shown to enhance the success of conventional glaucoma surgery in high-risk patients by inhibiting scar tissue formation over the site of the tiny incision made to let minute amounts of aqueous humor leave the eye to lower intraocular pressure. The purpose of this trial is to define further the safety and efficacy of this treatment.

Another surgical approach to the treatment of glaucoma is through the use of lasers. Numerous previous studies supported by the NEI have documented the efficacy, relative safety, and potential risks of argon laser trabeculoplasty, a procedure that increases outflow of aqueous humor. A randomized clinical trial, the Glaucoma Laser Trial, is comparing the efficacy of this therapy with that of traditional medical treatment with topical drugs in newly diagnosed patients with primary open-angle glaucoma.

To improve medical treatment of glaucoma, attempts are being made to find an effective carbonic anhydrase inhibitor—a drug currently administered in tablet form used in the treatment of some cases of glaucoma—that could be applied topically to the eye instead, thereby reducing its numerous undesirable systemic side effects.

A study is also being conducted to assess the value of home tonometry (the at-home use of an instrument that measures intraocular pressure) in glaucoma patients and ocular hypertensives (individuals with elevated intraocular pressure who do not have glaucoma but may develop the disease). This study may serve

to identify early those ocular hypertensive patients at risk for developing open-angle glaucoma and should enable physicians to treat glaucoma by prescribing optimal drug administration schedules to coincide with periods of elevated intraocular pressure.

### **Strabismus, Amblyopia, and Visual Processing**

Seeing involves a series of highly complex events that begin the instant light enters the eye and images fall onto the retina and continue until objects are perceived in all their detail, depth, and color. The act of seeing is always accompanied either by purposeful targeted eye movements or by searching and scanning movements. It is further refined by turning the eyes inward (convergence) when looking at nearby objects or outward (divergence) when looking at objects farther away. A disturbance of any one of the many parts of the elaborate and precisely controlled systems for ocular development, information processing, or eye movements can lead to serious vision impairment such as amblyopia (severely reduced vision in one eye often called "lazy eye"), strabismus (misalignment of the eyes—cross-eye or walleye), nystagmus (irregular eye movements), myopia (nearsightedness), defects in the field of vision, or other conditions that require very strong corrective lenses. These conditions collectively affect over 10 percent of the population. Although they seldom cause legal blindness, they produce considerable vision impairment and disability, interfere with learning and working, and even cause psychological problems because of their effect on appearance.

The NEI Strabismus, Amblyopia, and Visual Processing Program supports research on the structure, function, development, and disorders of those portions of the brain and extraocular muscle system that serve vision. These studies are directed toward gaining a better understanding of normal vision as well as determining the causes of visual deficits and blindness that do

not appear to be due to specific dysfunction of the eye itself.

Understanding visual processing and the disorders that affect it also provides valuable insights into the general functioning of the human nervous system. In fact, much of our knowledge of the workings of the brain have come through studies of the visual system. This includes molecular, cellular, genetic, and chemical aspects, how nerve impulses are transmitted and integrated, and the resultant perceptual and motor responses.

### *Effects of Early Visual Deprivation*

Studies of animal models of visual development and abnormal visual experience have contributed immensely to the clinician's knowledge and understanding of developmental visual problems seen in patients. An example is the concept of the "critical period" in visual development, which has made pediatricians and other clinicians treating children more aware of the importance of early diagnosis and treatment of visual problems, particularly of the need to follow closely the early visual development of infants. Recent clinical studies have focused on the development of visual acuity and resolution and color perception in infants.

New molecular research techniques have been used to label neurons in the central visual pathways of normal and visually deprived animals to describe the effects of visual deprivation at the cellular level. The realization that, at least in lower vertebrates, neural connections can be broken and formed by different manipulations has led to new concepts about the conditions required for the stable transmission of visual impulses. This work has expanded our understanding of the cellular basis of visual impairment caused by strabismus.

Priorities for future research in this area include identifying, characterizing, and defining the function of neurotransmitters, peptides and other chemicals important in signaling between cells in the visual pathways and oculomotor systems, and further describing at molecular,



physiological, and anatomical levels the development of the oculomotor system.

#### *Strabismus Treatment*

Each year more than 80,000 people undergo eye muscle surgery for correction of strabismus. One of the major problems confronting the surgeon is determining how much correction is required to bring the patient's eyes into alignment. Because it is difficult for doctors to gauge this precisely, many children with surgically correctable strabismus have to undergo several operations before alignment is achieved. To improve presurgical assessment of children with one common form of strabismus, the NEI is supporting a multicenter clinical trial that will determine whether children slated for strabismus surgery are more likely to have a successful outcome if the doctor first performs a prism adaptation test to estimate the amount of surgical correction required to achieve permanent alignment. This method may greatly reduce the number of repeat operations required for the correction of strabismus.

#### *Neural Regeneration in the Visual System*

A recent study has shown that adult retinal ganglion cells will regenerate injured axons for distances of several centimeters when they have been provided with a segment of peripheral nerve that has been grafted into the retina. This observation shows that peripheral nerves contain the necessary factors for regeneration that are not normally available to central nervous system neurons. These factors may include a suitable substrate over which to grow, as well as substances which serve to induce the alterations in gene expression that are necessary for axon growth. Identification of these factors may lead to the ability to stimulate the growth of new axons to replace those damaged by disease or injury.

Emphasis in future research activities will be on understanding factors that facilitate regeneration of optic nerve fibers and guide them to connect to the proper region of the brain; conducting neural transplanta-

tion research in mammals with the dual aims of eventually restoring lost visual function and, in the shorter term, learning more about the development of visual pathways in the brain; and using new imaging techniques, such as positron emission tomography or nuclear magnetic resonance, to localize lesions and test the functioning of specific parts of the visual system, especially "higher order" visual processing.

#### *Myopia*

Recent evidence has shown that near work can modify the resting tonus or state of contraction of the muscles that alter the shape of the lens to focus an image on the retina (accommodation) and those that move the eyes to allow binocular vision. This may contribute to the development of myopia. The role of sensory processes and oculomotor tonus in the control of visual accommodation and binocular vision is being investigated. Elucidation of the normal development of accommodation and convergence in human and nonhuman primate infants remains a research priority in this program.

Severe myopia has been produced experimentally in infant tree shrews; the myopic eyes also exhibit abnormal and retarded lens development. A study is being conducted to test the hypothesis that the growth of both the lens and the eyeball is regulated by the visual information received during development.

#### *Visual Rehabilitation*

A significant number of Americans have irreversibly impaired vision. In 1980, the National Society to Prevent Blindness estimated that there were 11.4 million people with impaired vision in the United States; of these, 1.4 million had severe visual impairment and about 500,000 of these were legally blind. In response to the needs of these people, the NEI is supporting research on the assessment of functional vision. The goal is to develop a battery of tests that could be used by eye care specialists to generate a visual function profile for each of their patients and then predict how their functioning will improve with the use of specific visual aids.

## **The Biennial Report of the Director, National Institute of Environmental Health Sciences**

### **History**

The following events represent milestones in the development of the National Institute of Environmental Health Sciences (NIEHS).

- November 1, 1966—The Secretary, Department of Health, Education, and Welfare, established the Division of Environmental Health Sciences as a part of NIH.

- January 12, 1969—The Division was elevated to Institute status and renamed the National Institute of Environmental Health Sciences.

- 1971—Dr. David P. Rall was named Director of the Institute.

- November 15, 1978—The Secretary, DHEW, announced the establishment of the National Toxicology Program (NTP) under the direction of the Director, NIEHS.

- November 20, 1985—The Institute was authorized by legislation in the Health Research Extension Act of 1985 (P.L. 99-158).

### **Introduction**

The National Institute of Environmental Health Sciences conducts and supports research, training, information dissemination, and other programs regarding factors in the environment that affect human health. The Institute investigates the health effects of chemical, physical, and biological environmental agents. Its goal is to provide the scientific information base, advanced scientific methodology, and trained manpower necessary to understand and ultimately prevent adverse effects of environmental agents.

Institute scientists, as well as grant- and contract-supported researchers, study the many different adverse effects toxic agents may cause. Potentially toxic agents can affect each of the major systems of the body (e.g., cardiovascular, central nervous, respiratory, reproductive, the immune system). Resulting adverse effects can be subtle, chronically debilitating, or acute.

These include, but are not limited to, neurological and behavioral disorders, respiratory disease, cardiovascular disease, biochemical and endocrine disturbances, kidney dysfunction, carcinogenesis (the ability to induce or promote cancer), mutagenesis (causing changes in the genetic material), reproductive disorders, birth defects, developmental disabilities, and subtle effects such as immune suppression. Lead exposure, for instance, may result in neurobehavioral effects, kidney damage, renal cancer, gastrointestinal effects such as abdominal colic, "lead line" on the gums, anemia, and hypertension. NIEHS concentrates research into all possible outcomes of the widest possible range of environmental exposures.

In its research, NIEHS seeks to identify and characterize potentially harmful environmental agents, particularly toxic chemicals. These studies include a variety of biological systems and test the results of carefully controlled exposures to hazardous agents. Which disease processes are initiated or aggravated by environmental agents and the extent of exposure of various population groups, especially sensitive populations, to these agents are documented. NIEHS supports efforts to identify hazardous agents before they are released into the environment. These include developing, testing, and validating biological assay systems to ascertain animal toxicity and, thus, to predict toxic effects which might occur in humans.

Information and new knowledge from NIEHS studies aids those agencies and organizations responsible for developing and instituting regulations, policies, and procedures to prevent and reduce the incidence of environmentally-induced diseases. For example, the Secretary of Labor recently set a timetable to establish standards for seven substances: asbestos, benzene, 1,3-butadiene, ethylene dibromide, formaldehyde, methylene chloride, and 4,4 methylenedianiline by the end of 1986. Of these seven, NIEHS studied all but formaldehyde for toxicity and carcinogenicity in its chronic assay



*A Toxicology Research and Training Program scientist uses electron microscopy in studies of heavy metal toxicology (above left). View of the NIEHS facilities in Research Triangle Park, N.C.*

systems; it found all six to be carcinogenic in rodents. This and other information is being used by the Occupational Safety and Health Administration (OSHA) to develop exposure standards to prevent harmful occupational exposures.

## NIEHS Programs

### Overview of the NIEHS Programs

To attack environment-related problems, NIEHS supports a broad spectrum of biomedical research, ranging from basic studies at the cellular and subcellular levels to more applied and clinical programs aimed at detecting toxic and other undesirable effects of various compounds used in industry and agriculture. This research is carried out at the Institute's headquarters in Research Triangle Park North Carolina, and through grants and contracts to various universities, research centers, and commercial facilities throughout the country.

There are four major research program areas, three of them in-house: the Toxicology Research and Testing Program (TRTP), the Intramural Research Program (IRP), and the

Biometry and Risk Assessment Program (BRAP). The fourth, the Extramural Program (EP), funds basic and applied research on the exposure of man and other biological systems to potentially toxic environmental agents; it also supports training in environmental health sciences research. Each intramural program is assisted by advisory boards composed of scientists from outside NIEHS. These advisory boards and the National Advisory Environmental Health Sciences Council (NAEHSC), which serves as the advisory board to the Institute's Extramural Program, aid the NIEHS Director in providing direction and oversight to Institute efforts. The peer review mechanisms are designed to assure that research carried out in-house and supported through grants and contracts is of the highest quality. Together, the four major NIEHS scientific divisions cover the spectrum of research opportunity in environmental health sciences.

## **Toxicology Research and Testing Program**

The Institute's Toxicology Research and Testing Program performs qualitative and quantitative toxicology studies to determine whether or not a chemical is potentially hazardous, how toxic it is in laboratory animals, and what its adverse effects are on human health. It is the principal focus within the National Toxicology Program for evaluating environmental agents for toxicologic properties, as well as for developing more efficient, effective, and less costly study methodologies. NTP is a DHHS interagency program established in 1978 to integrate activities and resources concerned with determining the toxicologic potential of chemicals and to forge stronger links between toxicology research and regulatory needs.

A second component of TRTP's work is the ongoing effort to develop newer, faster, and less expensive ways to determine whether substances are hazardous. Most current methods are expensive, time-consuming, and often not adequately sensitive. Yet the large number of new chemicals entering the marketplace each year makes it imperative that more efficient and accurate means of determining safety be developed. As an adjunct to its work on developing short-term *in vitro* and *in vivo* tests to supplement and, in some cases, supplant whole animal studies for identifying potential carcinogens, TRTP scientists are studying which assay systems, or combination of systems, are most effective in identifying potential carcinogens and noncarcinogens. Another objective is to develop a better understanding of the mode of action of carcinogenic chemicals that act through nongenetic mechanisms. Through this evaluation, TRTP expects to be able to define better the limits of predictability of these short-term assay systems.

Concurrent with this evaluation, TRTP continues to focus on improving the toxicological characterization of chemicals. The ability of environmental agents to affect genetic material, the reproductive process,

the immune system, and other major target organs is of great scientific and public health importance; therefore, TRTP researchers have initiated a comprehensive approach to toxicological evaluations. Numerous endpoints or potentially toxic effects, rather than a single result such as carcinogenicity, are examined. Through these efforts, TRTP scientists focus on expanding the spectrum of toxicological information about potentially hazardous chemicals and developing and validating the experiments and protocols most appropriate for regulatory and public health protection needs. TRTP provides much of the basic scientific information used by regulatory and other public health agencies to understand which chemicals may be public health hazards and what types of efforts should be initiated to prevent or reduce harmful exposures to them.

## **Intramural Research Program**

Scientists in the Intramural Research Program study the mechanisms of action of environmental agents found to be toxic to understand how such substances affect the living process. Using the latest techniques and equipment, they employ many scientific disciplines as they attempt to unravel events at the cellular and subcellular level. Their goal is to obtain insight into how hazardous substances affect cells, metabolic processes, and vital organ systems so that means can be developed to interrupt the biologic reactions and prevent the outcomes of exposure.

In focusing on this goal, IRP scientists concentrate on examining the biological basis of toxicology. Using the disciplines of genetics, neurobiology, pharmacology, pulmonary pathobiology, and molecular biophysics, they attempt to solve problems related to reproductive biology, cellular pathology, and neurobehavioral systems.

IRP research is based on the knowledge that the body's functions are controlled by complex interactions among four basic communications networks that govern the structure and function of all other tissues

in the body: the brain or neuroendocrine system, the immune system, the reproductive system, and the hormone or endocrine system. Each of these systems communicates with the others in a moment-to-moment, reversible and dynamic fashion in response to the ever-changing set of environmental signals (light, sound, touch, and chemicals). When all are working properly, the communicating systems respond in an integrated fashion, inducing adjustments in literally every part of the body down to the most minute component of each cell. Continual exposures to hazardous or toxic substances in the environment can cause adaptive responses within the body (a protective mechanism) to become difficult or even impossible. The result of this failure to respond often leads to a debilitating disease or, if the change is irreversible, death.

## **Biometry and Risk Assessment Program**

Scientists in the Biometry and Risk Assessment Program plan and conduct basic and applied research in the areas of quantitative and biochemical risk assessment, statistics, biomathematics, and epidemiology. Major focuses of their research are qualitative and quantitative estimation of adverse health effects resulting from exposure to potentially hazardous environmental agents, as well as development of methodology useful in this estimation process. Attention also is directed toward identifying environmental risk factors and elucidating the biological mechanisms that underlie their action.

In support of these goals, BRAP scientists in the statistical and mathematical section conduct a broad research effort involving the design and analysis of carcinogenicity experiments, statistical studies in genetic toxicology, mathematical modeling of various biological phenomena at the molecular level, and risk assessment methodology development. Scientists in the epidemiology component initiate field studies of human disease, particularly chronic diseases, attributable to environmental pollutants; investigate the effects of environmental toxins

on fetal and child development; and conduct basic and applied research in laboratory support methodology involved in the monitoring of human populations. BRAP researchers in the biochemical risk analysis section are concerned primarily with development of laboratory procedures for quantifying exposures in terms of the biologically effective dose, as well as with application of these procedures to human population monitoring and enhanced extrapolation of toxicologic outcomes across species.

### **Extramural Program**

The Extramural Program funds biomedical research and training in numerous disciplines related to environmental health sciences throughout the country. By means of NIEHS research grants, program projects, centers, fellowships, training grants, and other mechanisms of support, a cadre of scientists at universities and research centers concentrate on the prevention, diagnosis, and treatment of a variety of environmentally induced diseases. Some of the problem areas that are dealt with include neurological and behavioral disorders, respiratory disease, cardiovascular disease, biochemical and endocrine disturbances, kidney dysfunction, carcinogenesis, mutagenesis, reproductive disorders, birth defects, and developmental disabilities. NIEHS-supported scientists focus their research efforts on effects produced by chemical and physical agents at the molecular, cellular, tissue, and organ levels. This is a broad area of inquiry that integrates the traditional disciplines of anatomy, physiology, cell biology, endocrinology, genetics, biochemistry, reproduction, and epidemiology.

Through its Environmental Health Sciences (EHS) Core Centers and Marine and Freshwater Biomedical Sciences (MFBS) Specialized Centers of Research, the Institute provides long-term support for interdisciplinary study of the mechanisms of many environmental diseases. These centers aggregate small but highly skilled groups of scientists committed to research and teaching in the environmental health sciences

field. Moreover, the centers represent national resources that can be called upon to respond to acute emergency events, as when they provided scientific information following the sudden eruption of the Mount St. Helens volcano in May 1980. The influence of the centers is felt through the extent to which their scientists are called upon to provide guidance and advice in environmental health matters to international bodies; all the national agencies; to local, state, and regional bodies; and to the public.

Individually, the centers focus research upon one or more broad scientific areas such as: occupational and industrial health; heavy metal toxicity; agricultural chemical hazards; air, water, and food pollution; and the use of aquatic organisms as models of human systems and mechanisms of chemically induced diseases. The centers also study specific scientific problems such as how environmental agents cause cancer and birth defects; basic toxicity mechanisms; behavioral anomalies; respiratory and cardiovascular diseases; specific organ toxicology; body defense mechanisms; and how factors such as age, nutrition, and genetic makeup influence the expression and severity of toxic effects.

Teaching at a variety of levels also is supported at these centers to maintain and expand the pool of environmental health scientists. NIEHS supports training in the basic and applied research areas needed to determine risks associated with exposure to chemicals at an assortment of other universities as well. Training is provided in the areas of toxicology, pathology, mutagenesis, epidemiology, and biostatistics. Programs also are offered to train clinicians as environmental epidemiologists.

### **Major Research and Program Progress During Fiscal 1985-86**

Fiscal Year 1986 marks the 20th anniversary since the founding in 1966 of NIEHS as the Division of Environmental Health Sciences within NIH. Since that time, and

with the continuing support of Congress, the Institute has built a nucleus of scientists with unique expertise to address environmental health problems. At NIEHS, a strong core of scientific talent has been developed that is of international repute and can tackle concerns from a variety of perspectives. Centers for research have been established in universities throughout the country, and individual grants and contracts have been used to create a pool of scientific talent and vital scientific information that did not exist 20 years ago.

With this expertise, NIEHS has studied many chemicals with profound public health impact, such as asbestos, benzene, lead, DES (diethylstilbestrol), dioxin, and PCBs (polychlorinated biphenyls). Its scientists have increased our store of knowledge by showing, for instance, that asbestos can pose significant threats when inhaled, but is of far lesser risk when present in water that is ingested. NIEHS scientists also have clearly described some of the health risks of such ubiquitous substances as benzene.

While these contributions are enormous, as more and more chemicals and other potential toxins are introduced or identified in our environment, the task of studying each of these becomes increasingly difficult given finite resources of staff, time, and money. As a result, much of the Institute's effort is directed toward studies of the basic mechanisms of action by which these agents adversely affect human health, toward development of ways to predict harmful outcomes by studying common characteristics of known toxins, and toward development of test procedures that are more efficient and less costly.

The following section gives brief highlights of research progress accomplished by scientists in the four major NIEHS programs.

### **Toxicology Research and Testing Program Research Highlights**

- For the past several years TRTP, through the NIEHS and the National Toxicology Program, has been evaluating the toxicology of a number of chemicals found in toxic

waste dumps, the most hazardous of which are to be cleaned up under provisions of the "Superfund" legislation (P.L. 96-510, the Comprehensive Environmental Response, Compensation, and Liability Act of 1980). NIEHS works closely with the Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) of the Public Health Service in this effort. One of the compounds TRTP has studied under the Superfund program is benzene, long recognized as a cause of human leukemia. In studies by TRTP, benzene clearly caused cancers at a number of different organ and tissue sites in male and female mice and rats. The results of these studies support the carcinogenic effects seen in humans and should permit better prediction of human risk from benzene exposure; they also contribute to the knowledge base necessary for determining appropriate public health and environmental action with regard to toxic chemical dumps.

- Another compound TRTP has studied is methyl isocyanate (MIC), the chemical which caused thousands of deaths and injuries in Bhopal, India, when it escaped from a pesticide manufacturing plant. In TRTP studies of the immediate and delayed effects of acute inhalation exposure, methyl isocyanate at toxic levels caused severe damage to the respiratory tract of rats and mice but no damage to other organs. The experiments showed that methyl isocyanate was corrosive in the lungs, killing surface cells that then clogged the airways as they were shed, and caused inflammation and some fibrous growth, not unlike some of the effects of pneumonia. A second level of damage to the lungs was scarring, which impaired lung function. The results indicated two periods when the exposure was most likely to cause death: 4 days after exposure and again 8 to 12 days after exposure. One of the more positive findings so far is that methyl isocyanate did not appear to extensively harm the ability of exposed animals to have normal offspring, nor did it cause birth defects.

- In other work, TRTP has expanded experimental designs of long-term toxicology and carcinogenesis studies and made them more flexible, permitting provision of better data for low-dose extrapolation and hazard assessment while retaining the ability to detect a carcinogenic response in rodents. Shorter-term experiments also have been incorporated into the experimental design of long-term studies to enhance detection and characterization of nontumor toxicity.

- Nearly 2 billion pounds of 1,3-butadiene are used per year in the United States as an intermediate in the production of elastomers, polymers, and other chemicals. Approximately 62,000 workers are exposed annually to this colorless gas, with the majority of exposures occurring at sites of manufacture of elastomers and polymers using butadiene (e.g., synthetic rubber products). In a recent TRTP/NTP inhalation study with mice, butadiene was found to induce neoplastic lesions at multiple target sites at exposure levels below the threshold limit value for this chemical. Following release of these findings, EPA initiated a review of the chemical and concluded that the manufacture of 1,3-butadiene and its processing into polymers present an unreasonable risk of injury to the health of exposed workers, and referred it to OSHA for possible regulatory action. On April 11, 1986, OSHA announced it has determined that the magnitude of the carcinogenicity evidence in the NTP animal studies warrants regulatory action to protect the occupationally exposed population.

- In other TRTP/NTP studies methylene chloride, a solvent used for paint stripping, has been shown to be carcinogenic in mice and rats. Rats developed mammary tumors primarily, while mice were afflicted with liver and lung lesions. These test results were used by EPA in deciding to initiate a priority review of the chemical. Recently FDA published a rule to ban the chemical's use in cosmetic products, and OSHA is considering a number of actions for decreasing exposure to this chemical in paint strippers and spray paints.

- The toxicology and carcinogenicity of a class of dyes derived from benzidine were studied using approaches developed by scientists from the EPA, Consumer Product Safety Commission (CPSC), OSHA, NTP, National Center for Toxicological Research (NCTR), and National Institute for Occupational Safety and Health (NIOSH). This is permitting establishment of a set of basic principles to provide much of the scientific information required for making regulatory decisions concerning exposure to this class of compounds.

### **Intramural Research Program Research Highlights**

- IRP scientists have learned that man-made toxic agents such as phorbol esters and diethylstilbestrol (DES) mimic the actions of many naturally occurring growth-promoting hormones but in ways that lead to abnormal growth of cells. In intramural studies these chemicals are being used as experimental tools to broaden understanding of the ways in which some factors increase the sensitivity of biological systems to chemical insults. Phorbol esters, which are being studied because they represent a class of well-known tumor promoters, are structural counterparts to the fatty substances in our bodies that normally serve as mediators of growth-promoting hormones. Unlike these normal body fats, however, phorbol esters are not metabolized or deactivated by the host cell. From such findings, it is apparent that the dynamics of hormone action is an important determinant in how the body responds to environmental insults.

- In contrast to the phorbol esters, DES is metabolized in cells. (DES is a synthetic estrogen formerly used as a growth stimulant in animal feed, as a drug to prevent miscarriages and premature births, and as a postcoital contraceptive in humans.) Sometimes, unfortunately, this metabolism leads to the production of powerful agents called free radicals that can alter the structure and function of many cellular constituents including DNA, the genetic blueprint for the cells. DES uptake



by cells also can lead to damage to the nuclear chromosomes, which contain the genes or hereditary factors, and to the normal processes of mitosis, or cell division, resulting in tumor promotion. These findings suggest that alterations of the levels of free radicals may be of potential usefulness for preventing adverse effects of both man-made toxicants and natural body hormones.

- DES can initiate other processes through different pathways leading ultimately to marked changes in the ability of the human to function. One of these changes concerns the immune system. In IRP research, a correlation has been established in laboratory animals between administration of DES and other selected environmental chemicals, such as dioxins and benzo(a)pyrene, and altered immunological function. These changes in immunological function coincide with increased susceptibility to infectious agents and transplantable tumor cells in rodents.

- Cancer of the lung and lining of the chest cavity are dramatic effects of asbestos. The most frequent disabling effect, however, is fibrosis of the lungs. For this reason, IRP scientists are studying basic biochemical and cellular mechanisms of asbestos-induced lung fibrosis. Key findings from animal studies to date indicate that inhaled asbestos fibers small enough to reach the gas-exchanging regions of the lungs are deposited on the cell surfaces that line air spaces. Within minutes of deposition, these cells begin to engulf approximately 20 percent of the fibers and transport them to the inner walls of the air sacs where they interact with other cell types. The products of these cells, along with the asbestos fibers, produce an injury to the walls of the air sacs that is healed by fibrous tissue. The production of this fibrous tissue, which is an irreversible effect, has been found to impair normal lung function. Thus, this basic pathological reaction to asbestos is initiated soon after exposure and leads to the lung disease asbestosis. Because chronically asbestos-exposed humans and rats get essentially the same fibrotic lung disease, these results

provide evidence of the early critical events that initiate the disease process in humans.

- Improved understanding of gene structure and the role of chemical reactions between toxic chemicals or their metabolites and DNA helps explain how toxic agents affect genes and why genetic responses cause changes in cell structure and function. Through genetic and molecular studies on DNA metabolism as well as gene structure and function, IRP scientists are increasing understanding and improving evaluation of genotoxic health effects of environmental chemical and physical agents. Selected genes are studied at the molecular level to understand their organization, function, regulation, and evolution. Particularly important is the advancement of understanding of how genes are regulated during development. Considerable effort also is directed toward determining the nature and amount of genetic variability that exists in populations of organisms and the factors that influence this variability in both qualitative and quantitative terms. Recent discoveries of the surprising and diverse structures and functions of DNA are augmenting understanding of the effects of new mutations. Continued efforts in this area will provide a stronger scientific foundation for developing public health policies relevant to environmental genotoxic agents.

#### **Biometry and Risk Assessment Program Research Highlights**

- Chronic diseases contribute substantially to the morbidity of human populations and result in significant expenditures of public health dollars. Environmental agents may produce some of this disease, and identification of associations between exposures and certain diseases would presumably lead to the prevention of disease and death. Other than cancer, however, few chronic diseases have received much attention in studies of environmental hazards. BRAP epidemiologists are addressing the role of environmental factors in the etiology of some less studied chronic diseases. For example, chronic renal failure is a serious,

debilitating, and expensive disease that, for the most part, occurs without a known cause. A few specific environmental exposures like lead are known to be toxic to the kidneys at high doses, but the contribution of low-dose environmental factors over many years is not known. BRAP scientists currently are analyzing data from a case-control study of 709 patients with chronic renal disease to determine if exposure to a broad range of environmental agents may be linked to possible renal toxicity.

- Reproduction is one biological process that may be particularly susceptible to injury by environmental exposures. Animal studies suggest that early pregnancy may be a time of particular vulnerability to toxic substances. Recent developments in laboratory assays for early pregnancy make it practical for the first time to conduct epidemiologic studies of early pregnancy loss. A new radioimmunoassay has been developed for the pregnancy hormone, human chorionic gonadotropin (HCG), that can detect pregnancy by urine analysis as early as one week after conception. In a prospective study of 230 women who are trying to become pregnant, this assay is being used by BRAP scientists to test daily urine specimens for pregnancy hormone to detect subclinical pregnancy loss. The risk of such loss will be studied in relation to alcohol consumption, smoking, medications, and other common exposures.

- Components in cigarette smoke lead to adverse effects on the lung. While other health effects also have been linked to active smoking, possible consequences of passive or bystander exposure to cigarette smoke have only recently captured attention. Epidemiologists in BRAP have completed a study which suggests that persons married to smokers and persons whose parents smoked have an increased risk of developing cancer and other manifestations of tobacco-related disease. Cancer risk was found to be increased 60 percent among individuals married to smokers and 50 percent among individuals whose fathers smoked. Each of these exposures contributed independently



to cancer risk. The increased risk was not limited to known smoking-related sites, and was detected for both smokers and nonsmokers.

While these findings must be regarded as preliminary because of the small numbers studied, they do suggest that passive exposure to cigarette smoke may increase overall cancer risk and that risk may increase with increasing numbers of exposures. The findings are supported by several recent reports of increased lung cancer risk among nonsmoking women married to smokers and of increased cervical cancer risk among women married to smokers.

- In the area of cancer risk assessment, a number of issues relating to development of methodology useful in quantitative assessment of human health risks have been addressed. One of these is selection of the most appropriate dosage scale for extrapolation of risk projections across species based on comparisons of epidemiologic and experimental results. Development of quantitative risk assessment methodology also is being extended to include toxicologic endpoints other than cancer (e.g., teratogenesis or birth defects).

- BRAP investigators have used the large data base of TRTP/NTP carcinogenicity studies in a number of statistical research efforts. These include development of mathematical models for distribution of survival and tumor onset times for control animals; comparison of statistical analyses based on the overall proportion of tumor-bearing animals (all sites) with the usual approach of evaluating site-specific effects; investigation of interspecies correlation in carcinogenic response; assessment of the association between short-term (mutagenicity) and carcinogenicity test results for chemicals currently studied by NTP, and evaluation of the impact of using maximum tolerated doses on interpretation of study results. In the latter effort, data from 52 TRTP/NTP studies indicate that more than two-thirds of the carcinogenic effects detected in feeding studies (involv-

ing many different organ sites and tumor types) would have been missed had the high dose not been used.

- An epidemiologic study of 900 children to determine the effects of environmental contamination in breast milk on morbidity, development, and growth has found that more than 90 percent of the mothers have breast milk contaminated with polychlorinated biphenyls and DDT (stored as DDE). Results to date indicate that PCB and DDE levels decline over time spent lactating and that women with higher levels of DDE breast feed for shorter lengths of time. This study should provide insight into screening human populations for evidence of exposure to low, environmental levels of chemicals, as well as into measuring and understanding related early developmental effects.

#### **Extramural Program Research Highlights**

- University-based scientists supported by NIEHS grants are studying the dynamics involved in lead's effects at the cellular level. Although effects of lead on health have been studied extensively, scientists still do not know at what level of lead exposure significant health risk to people begins. NIEHS-supported researchers have developed new knowledge about the effects interactions of lead and calcium have on cell membranes and within cells. They have found that lead competes with calcium for sites on calcium-binding proteins located on mitochondrial membranes, the principal sources of cellular energy. When lead displaces calcium, energy used for specific cell functions is reduced or impaired. Lead also inhibits movement of calcium ions through voltage-dependent calcium channels in cell membranes. This cellular effect has been linked to the neurologic effects small levels of lead have on learning ability and behavior. Because of its effects on calcium-ion channels in cells lining the small blood vessels, lead probably interferes with regulation of blood pressure as well and may be a factor in hypertension.

- Other scientists supported by NIEHS are pioneering the use of a new method to measure the amount of lead in the bones of children.

This tool, which utilizes harmless x-ray fluorescence instruments sensitive enough to detect minute increases in lead, offers the possibility of determining minimal amounts of lead harmful to human health.

- For the past dozen years NIEHS has been supporting a major study investigating health effects of the principal constituents of air pollution in six cities, which represent a continuum of severity of air pollution. The study is designed to provide information on effects of ambient air pollutants on growth and development of children and on the general health, particularly with regard to respiratory disease, of both adults and children. Preliminary study results indicate that the frequency of coughs in children is associated with the average of 24-hour mean concentrations of air pollutants during the year preceding their health examinations. Rates of bronchitis and a composite measure of lower respiratory illness also are significantly associated with average particulate concentrations. The choice of study populations from cities with air quality exceeding as well as significantly below the National Primary Air Quality Standards has confirmed the effectiveness of current air quality standards. For the future, the most important aspect of this six-city study is that its longitudinal nature (i.e., identification and periodic followup of the same subjects) permits development of critical age- and sex-related data bases not previously available for the United States. This will enable scientists to evaluate risk factors and develop the most effective prevention strategies possible. Because the study also is one of the first studies to identify and compare health risks of indoor air exposures with those of ambient air exposures, its results should help frame site-specific regulatory and prevention measures.

- Another important aspect of the six-city study is that it made possible development of an operational monitoring system for sulfate/sulfuric acid aerosol measurements. These

pollutants are key components of acid rain. The monitoring system is to be deployed in each of the six study cities; and it will provide valuable measures of population exposures.

- In the course of gathering health information related to air quality in the six-city study, information on cigarette smoke exposure was assembled to rule it out as a variable which might have an effect on health and thus confuse interpretation of the environmental quality monitoring data. Information regarding cigarette smoking was analyzed, and it was learned that sidestream cigarette smoke may increase respiratory illness and result in a demonstrated decrease in lung function. In addition, the height of children of smokers was adversely affected, but their growth rate was not.

## Research Needs

While the Institute has supported and carried out research that has added enormously to our knowledge about the toxic effects of environmental agents, much remains to be learned. To help chart the future course for NIEHS, the National Advisory Environmental Health Sciences Council (NAEHSC), at the request of Congress, convened the Third Task Force on Research Planning in Environmental Health Science to assess needs and opportunities for research in environmental health sciences. Those areas of research promise in which scientific advances can be expected to have the greatest impact on preventing or alleviating environmental health problems of the coming decade are summarized below.

## Molecular and Cellular Mechanisms of Environmental Effects

The cell is the unit structure in living organisms; it is in the cell that effects of natural and synthetic toxic environmental agents unfold. Because of recent developments in cellular and molecular biology, scientists now have available powerful new concepts and techniques for studying normal behavior of cells

and responses of cells to environmental agents. These developments can greatly improve understanding of mechanisms of environmentally provoked disease.

Particularly promising are: (1) studies of the effects of environmental toxicants on cellular metabolism, growth, regulation, differentiation, and homeostasis or stability; (2) investigation of the role of changes in the cell membrane and cytoskeleton, or connecting network within the cytoplasm of the cell; (3) further analysis of the role of effects on the cell's genetic apparatus; (4) study of the role of free radicals in toxicant-induced injury; (5) examination of sequential responses to toxicants; and (6) study of the influence of such extracellular processes as immunological, endocrine, and other modifying factors. This research should add substantially to knowledge of how cells defend themselves against particular environmental agents, laying the foundation for essential prevention and regulatory measures.

## Reproductive and Developmental Effects of Chemical Exposures

Particular cells of interest to environmental health scientists are those involved with human reproduction. Survival of the human species depends on the integrity of the reproductive and developmental processes by which genetic information is transmitted to the next generation. But a growing number of environmental agents are known to disturb one or more of the interconnected functions involved in human reproduction. These processes range from gametogenesis, or the generation of male and female sex cells, to growth and development of the individual. Because effects on any one of these functions may interfere with normal reproduction, the entire spectrum of processes presents many targets for toxic insult. While understanding of the biology of these processes has increased dramatically in recent years, major gaps in knowledge persist.

To fill these gaps, the following research approaches deserve particular emphasis: (1) exploitation of advances in molecular, cellular,

developmental, and reproductive biology to further understanding of basic processes underlying normal reproduction and development; (2) investigation of absorption, distribution, metabolism, excretion, adaptive, and repair processes influencing susceptibility of the reproductive system and the embryo to injury by toxic agents; (3) development and validation of *in vitro* animal tests such as cell culture as model systems for investigating mechanisms of environmentally mediated changes and as screening methods for identifying agents that upset reproduction and embryonic development; and (4) identification and validation of methods for monitoring and assessing quantitatively the effects of environmental agents on human reproduction and development. This research will improve greatly our ability to identify agents that affect reproduction and enable us to estimate the risk of human exposure.

## Role of Immunological and Host Defense Mechanisms

Another target of toxic exposure is the body's immune system. Scientists have long known this system defends against invasion by infectious agents and spontaneously arising tumors, but now they know it must defend against toxic substances as well. Through traditional methods of toxicological assessment, scientists have learned the immune system is a frequent target organ of toxic insult following chronic or subchronic exposure to certain chemicals, therapeutic drugs, or radiation. Once threatened by these substances, the immune system may react with undesirable effects of three principal types: immune suppression, autoimmunity, and hypersensitivity. To better understand the nature of this response, mechanistic bases for effects of environmental agents upon host immune and defense systems must be defined in terms of current understanding of cellular and molecular biology.

To improve understanding of how environmental agents impact on the immune system, research of the

following types is needed: (1) expanded studies of mechanisms of toxicant-induced effects on immunity and their dose-response relationships; (2) enlargement of the data base on chemicals that alter the immune system to enhance knowledge of structure-activity relations and mechanisms and improve the capability for risk assessment and prevention; (3) further characterization of different immune disturbances induced by various agents with a view toward developing better methods for their early detection, diagnosis, and treatment; and (4) further development and validation of experimental methods to screen chemicals for immunotoxicity. Expansion of current knowledge about interaction of chemicals with immune and host defense systems will permit more appropriate decision making on chemical usage and risk assessment, as well as provide the foundation needed for understanding structure-activity relationships and mechanisms of chemical-induced damage.

### Genetics

Other chemically induced damage results from effects of environmental agents on the genetic architecture of life systems, which is of central biological importance. Scientists now know that damage to genetic material by environmental mutagens produces both immediate and long-term deleterious effects. These effects may upset the development and function of individuals through modifications of genes and chromosomes and be transmitted to future generations through mutational changes, adding considerably to the burden of disease.

Through remarkable technical advances in recent years scientists are able to characterize in detail fundamental genetic components of the cell, the coiled ribbon of DNA that contains instructions for all the cell's vital functions. These new techniques are being exploited to advance understanding of genetic mechanisms at the molecular level. They already have produced some important discoveries about gene structure and function that have profoundly changed our views about mechanisms of gene mutation, regulation, and transmission. Research in

the next few years must be designed to extend these new discoveries and relate them to solution of environmental health problems. Already a better understanding of genes and how they work is helping environmental scientists identify environmental hazards; predict which people are susceptible to them; and develop means for preventing, mitigating, or curing environmentally provoked illnesses. Within the next several decades, scientists may learn how to repair or replace abnormal genetic material in cells of those who suffer from genetic illnesses.

Many research approaches toward this end merit expanded support; among them are: (1) studies to determine more precisely molecular mechanisms of mutagenesis, chromosomal aberrations, and DNA repair; (2) studies on the biological significance of cytogenetic or chromosomal and gene abnormalities and their utility as indices of exposure to environmental toxicants; (3) longitudinal studies in genetic epidemiology to determine the existing burden of transmitted mutant genes and assess the impact of new mutations on human health; and (4) development of specialized registries and repositories for data, cell lines, and reagents that are of strategic importance in laboratory, clinical, and epidemiological investigations on genetic aspects of environmental health.

### Dose and Species Extrapolation

Epidemiological studies are important in many areas of environmental health research because data obtained from them provide the most reliable means of assessing human population risks from exposure to environmental agents. Unfortunately, relatively few environmental risk factors have been identified with a high degree of precision. Because few acceptable epidemiologic data exist for cancer caused by certain medicinal drugs and industrial chemicals, for example, it is necessary to rely to a considerable extent on relevant data from laboratory animals or other surrogates for predicting whether environmental chemicals are car-

cinogetic. Although laboratory experiments usually do not provide a full or certain answer of how a substance will behave in human tissues, all mammals share similarities in anatomical structure and metabolism, increasing the probability that results of a study in laboratory animals will predict a similar response in humans. The use of animal data to extrapolate from, or predict, human health effects, however, is complicated. It is made even more so by the necessity to extrapolate across species and across dose and exposure conditions.

To lessen the uncertainty involved in extrapolating human experience from animal data, further research along the following lines is called for: (1) studies to define the types and mechanisms of toxicity produced by different agents in different species, including humans, to guide investigators in selecting the appropriate dose-response model for use in estimating risks at low levels of exposure; (2) comparative animal and epidemiological studies to measure the predictive accuracy of animal tests; (3) analysis of the relative importance of different measures of toxicity in animal experiments; (4) further development and validation of short-term and *in vitro* tests to support, amplify, and extend whole-animal assays; (5) assessment of the extent to which variations in duration of exposure may influence the ultimate impact of a given dose of toxicant; and (6) investigation of interactive effects of exposures to multiple agents encountered in varying numbers and combinations. But even when the recommended research is carried out, uncertainties are likely to persist in dose and species extrapolations. Progress in the ability to assess risk of toxic effects, whether by carcinogens or other toxicants, will have to come from better understanding of the biology, pharmacology, and toxicology of environmental agents.

### Differences Among Individuals in Response to Environmental Agents

The nature of individual susceptibility to toxic effects is an area of

great biological importance and must be better understood. Scientists recognize the large degree to which individuals may vary in susceptibility to different toxic substances. This variability is of profound importance not only to the affected subjects, but also to those concerned with establishing safety factors for chemicals and other agents in the environment or the workplace.

Variations in susceptibility depend in large part on differences in the way substances are metabolized in the body. Added to this are individual factors, including heredity, age, sex, diet, drugs, smoking habits, occupation, lifestyle, and health status, which contribute to variation.

Effects of heredity on differences in susceptibility are particularly marked, often outwardly inapparent, and relatively little studied thus far. For this reason, and because powerful new methods have become available recently for investigating heredity (or pharmacogenetic) differences, these variations deserve particular emphasis in future research.

Promising approaches for studying such variations include: (1) review of drugs or other compounds to serve as suitable indicators of metabolism; (2) studies—exploiting newly developing antibody techniques and supported by development of appropriate registries, repositories, and data banks—to characterize in detail the complex enzyme systems responsible for metabolizing foreign substances; and (3) use of the new methods and reagents to characterize human populations with particular reference to identifying high risk individuals, as well as determining the precise nature and health implications of particular metabolic variations. Although these approaches need to be applied to human beings as effectively and rapidly as possible, they also will be useful in, and often facilitated by, parallel studies in animal models.

### **Pharmacokinetic Factors in Chemical Exposure**

To understand fully the health implications of environmental agents, scientists also must understand how they are handled in the body. Toxicity produced by an environmental agent in the body is mediated by interactions between the substance or its metabolite(s) and biological molecules or structures. It also is generally related to the concentration of toxicant and the time it stays at its site(s) of action. These factors, in turn, depend on such variables as route of exposure, dose, dose rate, and handling of the substance and its metabolites through the processes of absorption, distribution, metabolism, and excretion.

Pharmacokinetic models (or models of absorption, distribution, metabolism, and excretion) for describing quantitative and temporal relationships among these factors have been used systematically in the development and toxicologic evaluation of drugs. They have yet to be exploited fully, however, in the design, interpretation, and analysis of toxicological studies. Continued application of pharmacokinetic approaches to toxicological studies would enhance the ability to predict the effects on toxicity of such factors as exposure by different routes of administration, extrapolation of data to other species including humans, and extrapolation from exposure levels used in the experimental situation to those observed in occupational settings.

Research that must be pursued includes: (1) more extensive understanding and broader use of pharmacokinetic approaches in environmental health research to improve predictions of the extent to which toxicity of a substance may be influenced by variations in dose, dose rate, routes of exposure, presence of other substances, species, metabolism, and other variables; (2) further use of pharmacokinetic concepts for better assessment of toxicological risks in the human environment; and (3) future research focused on dose-dependent, nonlinear, and time-

dependent processes; interactive effects of multiple exposures; and development and validation of mechanistic models relating concentration of a toxicant at its target site to probability of a toxic effect. Such research will enhance the ability to accurately predict toxic effects of particular environmental agents and perform assessments of risk from human exposures.

### **Markers of Chemical Exposure and Preclinical Indicators of Disease**

While the above models will improve risk assessment capabilities, risk assessment methods must be supplemented with techniques for accurately measuring chemical exposure or with preclinical indicators that serve as forewarnings of susceptibility to disease or as early signals of disease. During this century the focus of major public health problems has shifted from infectious to chronic diseases. Chronic diseases are widely presumed to have multiple causes, multiple stages, and long latencies, while infectious diseases are linked more directly to specified, acute exposures to usually identifiable agents. To prevent chronic diseases, techniques have been developed to estimate the contribution of specific toxicants to increased risks. As tools for assessing risks, animal bioassays or *in vitro* test systems, however, do not provide sufficiently precise indicators.

For this reason, there is much need for biochemical, cellular, and physiological markers that can signify whether an individual has been exposed to a toxicant, quantify the extent of exposure, characterize the susceptibility of the exposed person, and identify preclinical signs of any resulting injury or disease at a stage when the process is readily reversible. Through recent advances, methods for some of the above purposes are becoming available. For example, by carefully analyzing body fluids, tissues, and cells, it is now possible to detect the presence of potentially harmful chemicals or toxicological responses (such as mutations or chromosomal aberrations).

Further research will be needed to validate the methods adequately, standardize them for routine use,

and refine them sufficiently for measuring environmentally important toxicants at levels resulting from normally encountered exposure conditions. The following are some research approaches meriting special emphasis: (1) tests for mutagens in body fluids; (2) *in vivo* assays for mutational events in germinal and somatic cells; (3) longitudinal studies of the predictive significance of cytogenetic changes; (4) examination of blood cell components in serum and urine as indices of toxicant-induced injury to the respiratory tract; (5) evaluation of neurochemical and electrophysiological changes as indicators of nervous system damage; and (6) study of various laboratory, clinical, and epidemiological data as indices of toxicant exposure of the reproductive system or of preclinical effects on reproduction, growth, and development. Once it is possible to detect and identify these biochemical markers early, physicians may be able to prevent or lessen consequences of environmentally induced diseases.

### Future Opportunities

While issues inherent in meeting environmental health challenges are complex, at no time in history has there been such promise that scientific research can be translated into practical benefits for all. The primary cause for optimism comes from advances in knowledge and technology, sometimes collectively referred to as "the new biology" and "the biological revolution." This new biology is rapidly advancing our understanding of the basic nature of life. As the cell has revealed more of its mysteries, a new blueprint of possibilities for ensuring human health and well-being is emerging.

### Broad Areas of Opportunity

Scientists at NIEHS and at grant-supported universities throughout the Nation are using this new knowledge to address many areas in need of research that hold promise for scientific advances with major benefits for public health. These include the areas delineated by the Third Task Force on Research Plann-

ing in Environmental Health Science and described in the preceding section:

- Molecular and cellular mechanisms of environmental effects.
- Reproductive and developmental effects of chemical exposures.
- Role of immunological and host defense mechanisms.
- Genetics.
- Dose and species extrapolation.
- Differences among individuals in response to environmental agents.
- Pharmacokinetic factors in chemical exposure.
- Markers of chemical exposure and preclinical indicators of disease.

Studies are already planned in many of these areas; examples of some of the studies include the testing of chemical mixtures, study of the developmental biology of estrogenic chemicals, investigation of the molecular basis for cancer, and identification of chemicals responsible for genetic changes. These are described in more detail below; they are but a few of the research areas NIEHS will address in the coming years. Others that will be supported by the Extramural Program, for example, include: (1) study of early indicators of chemical exposure through use of adduct formation and other biological indicators of effects, such as changes in proteins and enzyme systems; (2) research on mechanisms of cell injury by chemicals, emphasizing applications of new technologies; and (3) epidemiologic study of unique populations that offer opportunities to validate both new technologies and biological indicators of health effects.

In addition, because information and methodologies that will be developed through NIEHS research is needed by the medical community, regulatory and research agencies, labor groups, and others, the information and technologies must be translated and transferred to those individuals and groups. NIEHS must continue to support the information collection and dissemination

activities of the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC), as well as devise other means of technology transfer. Besides disseminating annual reports, annual plans, technical bulletins, the *Annual Report on Carcinogens and Toxicology*, and carcinogenesis technical reports to approximately 6,500 individuals and organizations on the Institute's active mailing list, NIEHS has:

- Contributed to development of a large computerized data base on animal cancer bioassay results which, in addition to study results, contains information on other factors that are relevant to evaluation of bioassay data. Subsequently, the Institute published information on each of approximately 3,000 experiments (775 chemicals) in the data base in *Environmental Health Perspectives*.

- Jointly sponsored with industry a conference on managing conduct and data quality of toxicology studies, which drew over 600 participants from academia, industry, the medical community, and government. The conference provided an opportunity for participants to exchange current practices, concepts, and new ideas for managing the quality of toxicology studies which have a regulatory impact on both national and international levels.

### Planned Studies

#### *Toxicology of Chemical Mixtures*

A serious challenge facing modern toxicology is the study and evaluation of chemical mixtures that commonly occur in the environment. An equally complex task involves assessing multiple risks from exposure to such mixtures. Although many of the useful products in commerce, many occupational exposures, and most environmental exposures involve mixtures of compounds, evaluating chemicals for toxicity traditionally has been performed on discrete chemical substances. But now that scientists must evaluate combinations of substances from waste sites, formulations such as pesticides, contaminated drinking water, and diesel and engine exhausts, and because the infinite



variety of chemicals found in the environment cannot all be studied, methods of evaluating mixtures must be developed.

To begin to analyze effects of exposures to chemical mixtures, TRTP scientists are designing a series of toxicological studies on chemical mixtures representative of ground water contaminants resulting from hazardous waste disposal practices. Three areas of study will be pursued initially; they are investigation of: (1) health effects of drinking water contaminants, (2) frequency of occurrence of toxicological interactions, and (3) a mechanistic approach to study of toxicological interactions. The primary objective is to fill gaps in the toxicity data base of chemicals chosen for their frequency in waste dumps and their known toxic mechanisms involving target organs such as liver, kidney, the nervous system, and reproductive organs.

In addition to these laboratory effects, NIEHS has contracted with the National Academy of Sciences to prepare guidelines for design of *in vivo* studies to assess the toxicity of complex chemical mixtures. The report resulting from this study is likely to serve as the scientific basis for Federal and industrial policies on methods for evaluating exposures to mixtures. Furthermore, the results of this study should provide considerable assistance in setting priorities for toxicologic evaluation of chemical substances.

#### *Chemical Mixtures in the Microelectronics Industry*

One occupational setting in which chemical mixtures are of particular concern is the semiconductor microelectronics industry. This industry is receiving increasing public health interest because of its continuing rapid expansion, exposure of workers to low-level mixtures of some unusual but extremely toxic chemicals, and a high percentage of women in the workforce, which increases the possibility of adverse reproductive effects from exposure to hazardous substances. One of the principal issues relates to developing methods for detecting early, sensitive, and specific indicators of chronic low-level organ toxic-

ity. The main limitations in developing such methods are centered around an inadequate understanding of mechanisms of injury from a chemical alone—or in combination with other toxicants or interactive factors. Only through further development of these methods will detection of "silent" damage to specific cell, organelle, or biochemical systems from chemical mixtures such as those found in the semiconductor industry be possible. These methods, in addition to providing early warnings of target organ damage, ultimately may have application for delineating relationships between cell injury and death and the elicitation of carcinogenic responses within these organ systems.

To address these problems, TRTP efforts currently are focused on assessing the potential risk of systemic toxicity produced by interactive effects between chemicals in a highly sensitive subpopulation. Special emphasis is placed on continuing development of noninvasive early biological indicators of cell injury to detect chronic low-level toxicity from these agents in target organ systems under multi-element exposure conditions. One major approach involves identifying metal-specific patterns in porphyrinuria (derivatives occurring in protoplasm that form the basis of respiratory pigments in animals and plants) following exposure to chemicals found in the microelectronics industry. Previous interaction studies with rodents chronically exposed to lead, cadmium, and arsenic demonstrated highly specific porphyrin excretion patterns for these elements alone or in combination. These patterns are well-correlated with ultrastructural and clinical indices of target organ toxicity.

Recent TRTP studies with the semiconductor compound, gallium arsenide, demonstrated a porphyrin excretion pattern similar to that produced by lead. These data suggest the strong possibility of a lead-gallium arsenide interaction within the hematopoietic (blood cell) system, which would have health implications for semiconductor workers living in areas with elevated lead exposure. TRTP scientists will continue to

develop sensitive, specific biological indicators of systemic target organ effects so that ongoing chemical-specific injury can be detected before development of overt clinical disease.

#### *Developmental Biology of Estrogenic Chemicals*

Another group of chemicals of increasing public health concern is a large group recently discovered to behave in a weakly estrogenic manner, that is they possess the biological activity of the female sex hormone estrogen. The synthetic estrogen diethylstilbestrol (DES) is representative of this group. Environmental distribution of these estrogenic compounds occurs through two major sources: synthetic chemicals introduced as byproducts of civilization and naturally occurring estrogens found in numerous plants as well as in molds that infest stored crops. The structural basis of their estrogenic activity remains poorly understood.

To predict more accurately those chemicals that will exert estrogenic effects on exposed humans, IRP scientists are directing a major research effort toward characterizing the molecular structure common to this class of compounds. This area of research is important for such public health concerns as the premature sexual development reported in Puerto Rican children. So far IRP studies on abnormal development and cancer induced by estrogens have resulted in new insights regarding mechanisms of action of estrogens, including the ability of these compounds to permanently alter cell differentiation at the molecular level. Other studies of developmentally estrogenized laboratory animals and humans are providing new insights into basic mechanisms of sex differentiation, genital tract pathobiology, and hormonal carcinogenesis. This insight provides opportunities for development of new therapeutic strategies for cancer prevention in estrogen target tissues such as breast, cervix, and uterus, as well as different approaches to environmental monitoring of these compounds.



## *Molecular Basis for Cancer*

Another promising area in which understanding is growing rapidly and scientific opportunity exists is the study of the molecular basis for cancer. In the last few years, oncogenes, tiny pieces of DNA that may be part of the normal genetic makeup of human cells, have been uncovered. The riddle of why normal cells contain this material that, when altered by environmental agents ranging from cigarette smoke to viruses, may initiate the cancer process is still unsolved. But there is increasing evidence that conversion of a normal cell into a tumorigenic cell is a multistep process involving alterations in a number of genes. As scientists learn more about oncogenes, they are closing in on the hundreds of diseases we know as cancer. The challenge is to learn how oncogenes are altered and the role carcinogens play in these alterations.

Drawing on the Institute's unique capacity for carcinogenic studies in rodent model systems, BRAP scientists in collaboration with TRTP researchers have mobilized a research effort aimed at characterizing activated oncogenes and establishing approaches for using these data in analyzing health risk from exposure to certain classes of chemical carcinogens. Using animals exposed to carcinogens, these scientists are examining oncogenes which seem to be activated in an early stage of cancer. So far they have learned that when there is an insult to DNA by a carcinogen, these oncogenes are activated and begin to produce altered protein products or too much of the normal product. In trying to develop a better understanding of effects of chemicals on these genes, BRAP scientists hope to explain tissue and cell specificity of carcinogens, stages in the multistep carcinogenic process at which carcinogens are active, the relationship between spontaneous and carcinogen-induced tumors, the dose-response curves for chemicals particularly at low levels, and animal to human extrapolations. Through studies of the interplay required among oncogenes for a normal cell to be transformed into a malignant

one, scientists eventually may be able to classify carcinogens according to their mechanisms of action, enhancing our ability to estimate accurately the risk of cancer in humans exposed to carcinogens.

### *Genetic Effects of Toxic Chemicals*

Genetic effects of toxic chemicals are important not only for themselves but also because they may be precursors of carcinogenic effects. In the area of genetics, scientists supported through EP grants are attempting to discover which chemicals in our everyday environment actually cause genetic changes in people. In attempting to answer this question, they are capitalizing on two types of recent technological advances. First, it is now possible to identify and measure amounts of some environmental chemicals or their metabolites found attached to proteins and DNA in human tissues. With further research, it should be possible to identify many chemicals that actually enter the human body and are converted to forms capable of reacting with genetic material. Second, scientists have discovered that chemicals cause specific patterns of genetic change in human cells.

With this knowledge, NIEHS-supported genetic toxicologists are working on techniques to obtain patterns of genetic change from cells in ordinary blood samples. These patterns would be used as "genetic fingerprints." With knowledge of chemical derivatives actually found in a person's blood and genetic fingerprints from that same person, it should be possible to discover which, if any, of those chemicals found are responsible for causing particular genetic changes. Some of these approaches are being applied in pilot epidemiologic studies of selected populations. For example, individuals with known exposures to aflatoxins are having blood analyzed for DNA adducts (products of interaction of a chemical or its metabolites with DNA) by chemical means and by analysis of particular antibodies called monoclonal antibodies. Breast cancer patients treated with chemotherapeutic

agents with known mutagenic activity likewise are being studied.

These investigations will be expanded and extended to other populations as further technical developments permit. Should the technological efforts prove successful, they could identify which chemicals in our environment are responsible for genetic changes in humans. Such knowledge could serve as the foundation for a rational policy of regulation and public protection for future generations of Americans.

## **Policy Issues**

In addition to the scientific issues that capture NIEHS attention, a number of policy matters are of particular importance to the Institute. These include:

- The potential impact "Superfund" reauthorization will have on the Institute and its programs.
- The necessity to strike a balance between basic research and the demand to test for effects of currently troublesome substances (e.g., dioxin, MIC, EDB).
- The need to assess assumptions used in mathematical risk assessment and develop better indicators of exposure and damage.
- The requirement to balance the cost for maintaining facilities and purchasing equipment against needs for scientific research and investigations.

The Institute will be addressing these issues in the coming year.

# The Biennial Report of the Director, National Institute on Aging

## History

The following events represent milestones in the development of the National Institute on Aging (NIA).

- December 2, 1971—The White House Conference on Aging recommended the creation of a separate National Institute on Aging.

- May 31, 1974—The Research on Aging Act (P.L. 93-296) authorized the establishment of a National Institute on Aging and required that the Institute develop a national comprehensive plan to coordinate the HEW agencies involved in aging research.

- October 7, 1974—The National Institute on Aging was established.

- April 23, 1975—The first meeting of the National Advisory Council on Aging was held.

- July 1, 1975—The Adult Development and Aging Branch and the Gerontology Research Center, NICHD, were separated from their parent Institute to become the core of the National Institute on Aging.

- December 8, 1976—*Our Future Selves*, the research plan required by P.L. 93-296 for HEW-conducted and -supported aging research, was transmitted to Congress.

- 1979—Alzheimer disease research was designated the highest NIA priority.

- September 1982—The "National Plan for Research on Aging" was published.

- September 20, 1982—The NIA Laboratory of Neurosciences Clinical Program admitted the first inpatient to a new unit at the NIH Clinical Center.

- 1983—Dr. T. Franklin Williams was appointed Director of the Institute.

- September 9-11, 1983—The NIA celebrated the 25th anniversary of the Baltimore Longitudinal Study of Aging.

- 1984—The Alzheimer Disease Research Centers were established.



*NIA research is aimed at improving the quality of life, not simply by extending human lifespan, but by prolonging the active, independent years.*

## Introduction

The NIA is responsible for conducting and supporting research and training on the biological, medical, behavioral, and social aspects of the processes of aging and the problems and needs of older people, and for carrying out public information and education programs to disseminate the findings of this and other relevant research. The NIA also has the specific responsibility for conducting and supporting research relating to Alzheimer disease.

Although research on aging processes and the diseases associated with advanced age is still in the early stages, significant progress has been made in the last decade. Advances in Alzheimer disease, the highest research priority of the NIA, have been made both in diagnosis and in understanding of the basic mechanisms underlying the disease. The establishment of specialized Alzheimer Disease Research Centers has provided a rich environment for characterizing further this devastating disease and, ultimately, for identifying treatments.

Research emphasis is also directed towards understanding the most

basic mechanisms of aging. The NIA is also focusing attention on molecular genetics, utilizing new, powerful research techniques to identify and isolate genes responsible for age-related diseases and to investigate the genetic basis for differences in aging. The new NIA Laboratory of Molecular Genetics was established in October 1985. NIA scientists working in this laboratory will search for genes involved in aging processes and will examine the molecular basis for the age-dependent decline in immune function, the relation between aging and cancer, and alterations in the expression of certain genes which may play a role in Alzheimer disease.

In the area of health promotion, social and behavioral sciences research supported by the NIA suggests that the productivity of the middle years can often be extended and that many disabilities of old age can be prevented, reversed, or postponed. Studies have also shown that, even at advanced ages, health attitudes and behaviors can be modified and that benefits can be derived from such changes. NIA is encouraging increased research on

social and behavioral factors in health promotion and two important aspects of health maintenance in older people—nutrition and exercise. In the area of nutrition a primary goal is to define the nutritional requirements for good health in older people—a serious gap in the nutrition science base. In the area of exercise, recent studies have demonstrated major beneficial outcomes from systematic endurance-type training in most older men and women, and have indicated that even moderate exercise in older women can slow down the accelerated bone loss that predisposes to hip fractures. The NIA will focus its research efforts on understanding heart/lung function and physical fitness, skeletal-muscle performance and capacity, role of exercise in preventing bone loss, and the relation of psychological and social stresses and supports to health behaviors in older people.

Other areas of particular research emphasis include: causes of falls and fractures (specifically, osteoporosis and gait/balance disorders); systolic hypertension in older adults; special health needs of racial and ethnic minority members; demographic and epidemiologic studies of the population over 85 years—the fastest growing segment of the U.S. population; and continuation of the successful Baltimore Longitudinal Study of Aging.

The NIA's research agenda is multidisciplinary and broad in scope, reflecting the fact that aging research seeks to uncover new knowledge about the physical, behavioral, and social aspects of human aging. NIA participates in many collaborative activities with other Institutes at NIH and other Federal and non-governmental agencies. Research is aimed at improving the quality of life, not simply by extending human life, but by prolonging the active, independent years.

The NIA supports a wide variety of training opportunities to help individuals prepare for or advance their careers in research and training in aging and geriatrics.

## High Priority Areas

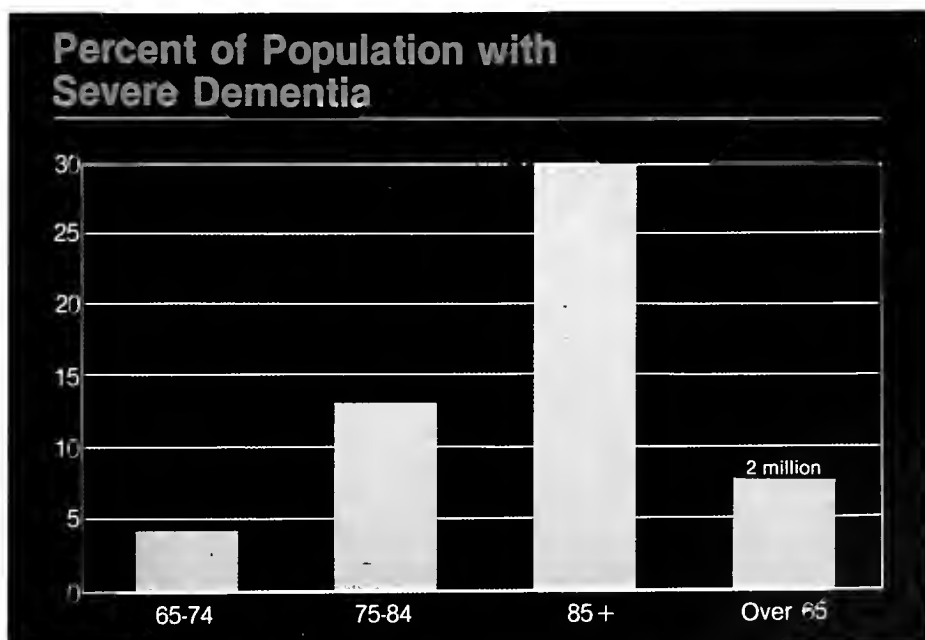
### Alzheimer Disease

Alzheimer disease (AD) is the most devastating disease of older persons. It is of epidemic proportions (affecting 2 to 3 million people, a number that is expected to double or triple in the next 15 years), and results in very heavy burdens on families and costs to society (an estimated \$38 billion in direct costs each year, a figure that will also rise proportionately). Although AD is not a natural and inevitable consequence of aging, its incidence increases with age. Research offers the only hope for finding answers that will relieve these burdens and costs. Scientific opportunities in molecular biology, genetics, protein chemistry, epidemiology, cognitive and social sciences, and other relevant fields are ready to be exploited.

The systematic study of AD was begun within the last decade, despite the fact that the disease was first described nearly three-quarters of a century ago. Our knowledge of this disease has advanced from nearly total ignorance to a level at which it is possible to formulate viable hypotheses to explain its causes and to begin testing potential treatments.

One of the major problems that impedes the progress of research in AD lies in the accuracy and sensitivity of diagnostic procedures. Recent major workshops on this topic (one national and one international), organized by NIA with multiple sponsorship, have helped to define the diagnostic issues and specify research opportunities in this area, including the identification of a plasma protein that can be used as a marker for AD; the possibility of locating membrane transport abnormalities in peripheral nonneural tissues; the development of better correlations between cognitive measures and data from brain imaging devices such as nuclear magnetic resonance (NMR) and positron emission tomography (PET); and the construction of more sensitive neuropsychological test batteries for detecting age decrements in memory and information processing.

Recently, one NIA grantee reported finding a unique protein, Alz-50, which appears to be a marker for degenerating nerve cells, found only in specific locations in the brains of AD patients and absent in other degenerative neurological disorders of the aged. This finding promises to provide an accurate

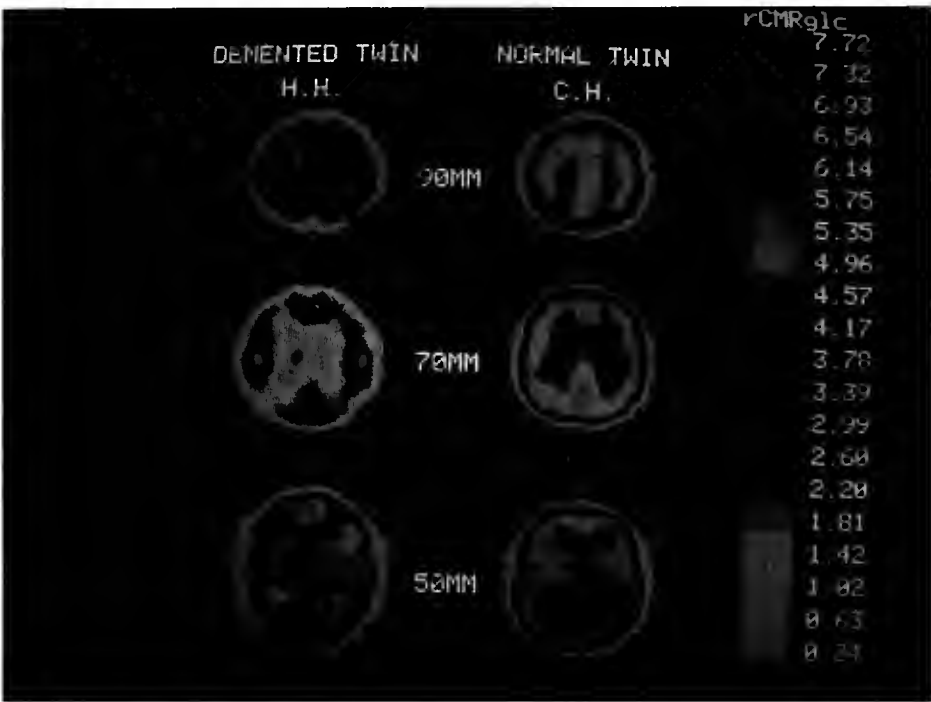


*Severe dementia, most of which is attributed to Alzheimer disease, is of epidemic proportions. This shows the age range of the population that is affected by the disease.*

ate diagnostic tool and offers the opportunity to explore the mechanism by which such abnormal proteins are made and are related to the disease process. Another grantee is using NMR to examine patients with AD and other forms of dementia. NMR's unique ability to distinguish the brain's white and gray matter allows it to pick up abnormalities that may indicate early multi-infarct dementia in patients in whom other technologies such as computerized transverse axial tomography (CT) scans did not detect these changes. Multi-infarct dementia is the second leading cause of dementia in older people.

NIA's intramural scientists have reported findings that hold considerable promise for early detection of AD: (1) the rate of brain atrophy (decrease in the percentage of intracranial space occupied by gray matter) as measured by CT is greater in AD patients than in healthy age-matched controls; (2) in patients with early AD who have only memory decrements, there is increased metabolic difference between the left and right cerebral hemispheres (as measured by PET), compared to controls; and (3) there is decreased concentration of a peptide, corticotropin-releasing factor, in the cerebrospinal fluid of AD patients.

In other areas, important progress has been made in separating, solubilizing, and identifying the precise composition of the abnormal proteins in the brain cells of AD victims. Through the techniques of molecular biology, it will soon be possible to identify the genetic and chemical mechanisms for the formation of these proteins. It should also be possible to distinguish the biological mechanisms of normal neuronal aging from those involving AD pathology through a better understanding of age-related changes in cytoskeletal organization, membrane protein alterations, and transport mechanisms. The genetic factors in the etiology of AD are a major area of research in 6 of the 10 NIA-supported Alzheimer Disease Research Centers (ADRC). The recent establishment of a cell bank



PET scan with fluorodeoxyglucose shows the decrease in glucose metabolism in the brain tissue of a 59-year old male with Alzheimer disease (on left) compared with his normal identical twin (on right).

from well-characterized patients with familial AD will help materially to address research in this area.

In addition to tangles and plaques—characteristic pathology related to nerve cell degeneration—AD brain contains deposits of an abnormal protein (amyloid) in and around blood vessels. An NIA grantee has isolated and analyzed the amyloid proteins circulating in the bloodstream of AD patients and has found a unique protein not seen in healthy individuals. Interestingly, the same protein appears in the amyloid deposits of Down syndrome, representing another link between AD and Down syndrome.

It has now been suggested that when the central nervous system is exposed to aluminum over long periods of time, the result is neurofibrillary tangle formation and ultimately cell death. An NIA grantee has found that aluminum binds to a protein (calmodulin) inside the nerve cell, thus impairing its ability to regulate calcium levels in the cell. Calcium is similar in structure to aluminum and is vital to

the life of the cell, but it is toxic in large quantities. The key to aluminum's deadly effect on nerve cells may be this breakdown of calcium metabolism at the cellular level.

Work continues on "slow virus" infections that cause certain forms of dementia in humans and in experimental animals. It has been shown that the protein (prion) involved in the animal disease "scrapie" is part of a larger protein present in both normal and infected cells. In normal cells, the larger protein is completely broken down by enzymes; in infected cells, defective breakdown leaves the prion intact. This protein has a fibrous structure that resembles certain filaments found in the brains of AD patients. Efforts are now focused on determining what happens to change a normal cell into an infected cell.

Recent research has shown the previously unrecognized plasticity and transplantability of the central nervous system and has begun to identify trophic factors and chemical messengers regulating nerve growth in the aging brain. With further progress in this area, treatment of AD becomes a more realistic goal.

Studies of relationships among patients, care providers, and family members promise to provide much needed information for the care of AD patients. Studies of family influence on the symptoms of AD may lead to means for alleviating the associated stresses.

There is a great need for comparative, longitudinal, community-based studies of dementia (including international, cross-cultural studies, as called for by the Secretary's Task Force on AD) that can provide clues to etiologies, define risk factors, delineate differing clinical features, and assist in the development of the strategies for early recognition. Examples of important research findings are those from the NIA's longitudinal epidemiologic study of a representative aging population in East Boston, which indicate a higher prevalence of significant dementia (approximately 37 percent of those over age 85) than has previously been documented and far higher than reported in some other countries, i.e., Japan.

Opportunities exist for utilizing other established population-based studies. NIA is already utilizing the Framingham Heart Study for this purpose and proposes to do the same in a followup of the Honolulu Heart and Cancer Study. Research groups in Sweden, Italy, Japan, and possibly other countries are interested in participating in such studies, with their own financial support for the most part; NIA would provide the core and coordinating support.

As mandated by Congress, NIA, in collaboration with other Institutes, has established ten centers of excellence for research on AD and related disorders (ADRC). These centers support new research and enhance ongoing research by providing core support to bring together biomedical, clinical, behavioral, and social investigators to enrich the effectiveness of AD research and, ultimately, to improve health care. They provide a strong environment for training additional investigators and disseminate AD information to both scientists and the public.

In the future, the NIA will focus its program development activities concerning AD and related dementias on the above scientific opportunities and the following areas: development of diagnostic instruments; neural transplantation and plasticity and neurotrophic factors; longitudinal epidemiological studies; protein chemistry of cytoskeletal elements, particularly that of filaments and microtubules; multicenter international studies to assess risk factors in the etiology of AD; development of monoclonal antibodies for specific proteins within the brain; study of brain enzymes, particularly those related to oxidative metabolism and synthesis of neurotransmitters; the roles of toxins and infectious agents on degenerative processes; genetic factors in neural degenerative processes; neuropharmacology of cognitive disorders; and social and behavioral factors in coping with the disease.

### Understanding Aging

#### *Molecular Genetics in Aging Research*

Powerful molecular genetic techniques are now being used by NIA-supported scientists to investigate mechanisms of aging and the genetic basis for differences in aging. Strains of various organisms with altered lifespans have been isolated, and studies are under way to determine the number and nature of genes responsible for observed differences. These genes may control either regulatory functions or enzymes which directly affect the rate of onset of aging; it will be important to identify both kinds of genes.

Recombinant DNA techniques are also used to study changes in gene structure and gene action with age to identify causal relationships between aging and cellular metabolism. Research findings include: (1) amplification of at least one known oncogene increases progressively with aging of fibroblast cultures; (2) DNA in livers of mice becomes progressively less methylated with age; and (3) microinjected oncogene DNA can induce proliferation in quiescent cells but not in senescent

cells. These results support the hypothesis that DNA structure and gene expression change with age and that proliferation of senescent cells is blocked in a unique way.

Molecular genetics also provides an opportunity to isolate and identify genes responsible for the onset of age-related diseases, such as familial Alzheimer disease. The demonstration of a familial form of this disease now makes credible the isolation of one or more Alzheimer disease genes, using DNA probes already isolated from specific regions of human chromosomes. Once a gene has been isolated it will be possible to determine the product of that gene, develop a better understanding of the cause of the disease, and possibly formulate an effective treatment.

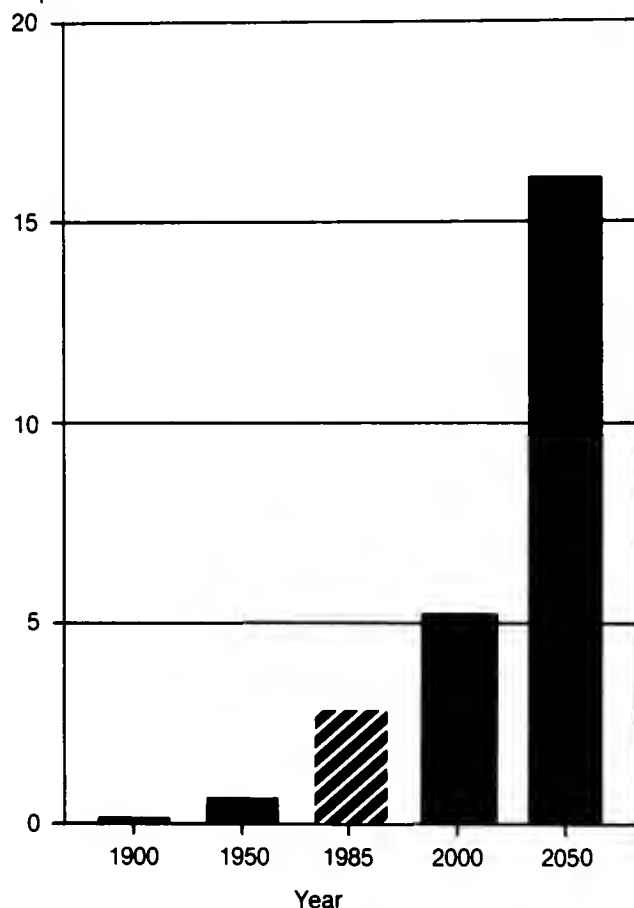
The NIA's intramural Laboratory of Molecular Genetics (LMG) is investigating the molecular basis for aging and age-dependent diseases including the decline in immune function that occurs with human aging. Investigators are looking specifically at the expression of the interleukin 2 gene. Interleukin 2 stimulates the clonal expansion of lymphocytes. Studies at the NIA's Gerontology Research Center (GRC) confirm that the production of interleukin 2 declines in lymphocytes from older human volunteers and attempts are being made to discern the molecular basis for this decline. Results may yield opportunities to slow down the immune decline with aging and help augment the response of older adults to infections. Other planned projects include an in vitro examination of the relation between aging and cancer development, an investigation of the effect of aging on gene expression in rat pituitary gonadotrophs, and a study of DNA repair in the isolated cell. The LMG will also focus on whether alterations in the expression of certain genes may play a role in Alzheimer disease.

#### *Demographic and Epidemiologic Studies of the Oldest Old*

The elderly population is aging. The oldest old (those 85 and over) are the fastest growing segment of the population; by one estimate they will constitute 5.2 percent of the

# U.S. Population 85 Years and Over

Population in Millions



Source: U.S. Bureau of the Census

*The oldest old, aged 85 years and over, is the fastest growing segment of the population.*

population by the year 2050. The decline in mortality at extreme ages partially accounts for this very rapid growth of the oldest old. Despite their heavy burden of morbidity, including a high level of cognitive impairment, and high use of services, little is known about their physical and cognitive functioning, comorbidity, and pathways to dependency, and whether the burden of morbidity will expand or contract. Progress in this area had been slow until the development of the NIA's oldest Old initiative and the subsequent issu-

ance in 1984 of a program announcement to stimulate research in this area.

Through interagency agreements with the Bureau of the Census and the National Center for Health Statistics (NCHS), NIA has helped to stimulate scientific efforts and to improve the availability of national data on the 85 and over population. The Bureau of the Census is preparing special tabulations on the 1980 census, investigating the quality of the 1980 census data on the very old, and developing an international data base on aging. The NCHS is

preparing a special historically organized data file for the analysis of trends, and is also conducting the Longitudinal Study of Aging that will provide important information on the transitions between independence and dependence for the very old.

Extramurally funded researchers are currently conducting studies of multiple causes of death, trends in morbidity, the demography and the rapidly changing composition of the oldest old, and cognition among the very old. Following a workshop on the Methodologies of Forecasting Life and Active Life Expectancy (the period of life an average individual can expect to remain independent and functioning without assistance), in March 1986 a Request for Applications (RFA) was issued soliciting research projects on the development of models for forecasting life expectancy, and assessment of competing causes of mortality and morbidity.

## *Baltimore Longitudinal Study of Aging*

The Baltimore Longitudinal Study of Aging (BLSA), conducted by the NIA intramural research program, is a unique resource to study the processes of human aging. The study population is a group of community-dwelling volunteers ranging from 20 to 95 years of age. The subjects, who are enrolled for their lifetimes, return to Baltimore every 2 years for reevaluation. Currently, there are 600 male and 346 female active participants. The male study is in its 29th year and the female study in its 9th year.

A longstanding recruitment goal for the BLSA study has been to increase the number of women to equal the size of the male sample. This would facilitate the search for precursors or risk factors in women and lay the basis for insights into the unexplained sex differences in disease development and longevity.

Participants are studied intensively for physiological and behavioral changes, patterns of age changes are identified, mechanisms underlying the changes are elucidated, disease-aging interactions are evaluated, and normative standards as influenced



by age are defined. Researchers have also begun to emphasize the need to consider the interacting influences of biological processes, personality and behavioral factors, social and environmental forces, and the idiosyncratic health behaviors and stresses of the individual.

Planned or recent collaborative BLSA studies include an autopsy program, an oral physiological component with the National Institute of Dental Research, neurological assessment of mental status and physical movements, and identification of individual differences in reactivity to drugs. Other studies will focus on osteoarthritis and the relation between physical activity and cardiovascular status.

New information about the effect of age on cardiac function during rest and exercise has come from BLSA investigations. After excluding subjects with occult coronary disease, scientists have found very little if any age-associated decline in cardiac output—the quantity of blood that flows from the heart each minute—but the results point to age-specific mechanisms by which the heart adapts to increased workloads. The screening techniques used for this study to detect asymptomatic coronary disease—thallium scanning and electrocardiogram (ECG) monitoring during exercise—show considerable promise as predictors of the likelihood of future coronary events, such as a myocardial infarction or angina. Further research is needed both to identify the mechanisms underlying the aging heart's adaptive processes and to confirm the predictive utility of these techniques. The results thus far indicate that in many people in their 70's and 80's cardiac function is and will be maintained at high levels.

#### **Hip Fractures, Osteoporosis, Falls, Gait Disturbances**

Hip fractures in older people are a major cause of mortality, morbidity, and health care costs in this country. It has been found that 84 percent of the more than 200,000 hip fractures that occur in the United States each year are in persons over age 65. Approximately one in five hip fracture

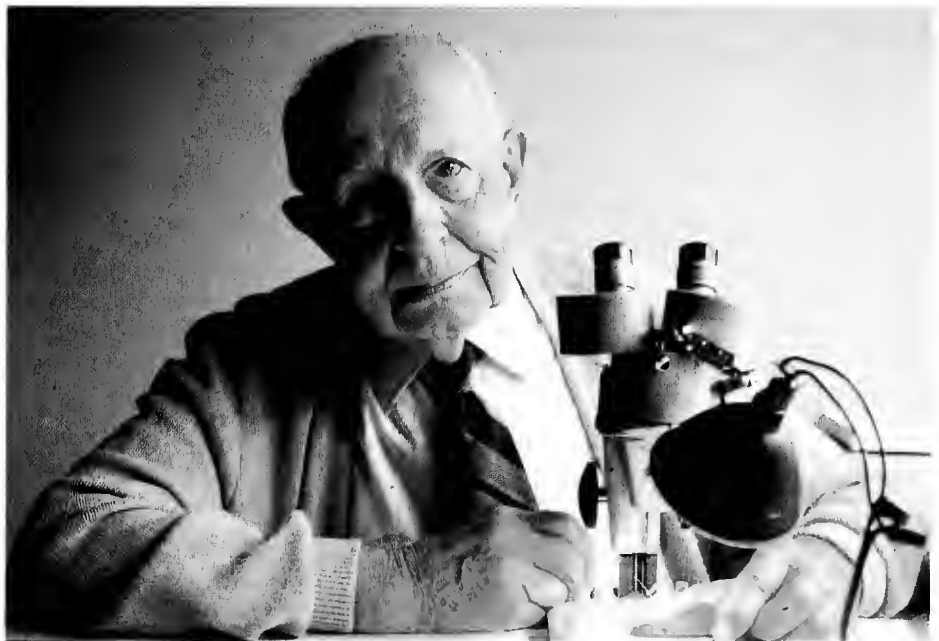
patients dies of complications attributable to the fracture. Of those surviving 1 year, about 25 percent do not regain independent ambulation. The annual cost of hip fractures has been estimated at \$7 billion which includes hospital, surgical, and physicians' fees, drugs, home health care, and long-term nursing home and rehabilitation costs.

Studies show that older people who fall are more likely to have a compromised balance response than their nonfalling counterparts. In late 1985, the NIA announced the availability of \$1.25 million for the study of neurologic, cardiovascular, muscular, and perceptual aspects of falls and gait disorders. We need to determine the underlying causes of disturbances in gait and balance in older people that predispose them to falls, and thus to hip fractures. Preliminary findings indicate that many older people may be prone to falls due to specific neuromuscular deficits that are potentially correctable.

Osteoporosis is a degenerative bone disease directly related to fractures and loss of mobility in older people. The disease affects more than 20 million people in the United

States and is a major risk factor for hip fracture. In cooperation with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIA sponsored a workshop on osteoporosis to identify important research questions. The two Institutes will issue a joint announcement in late 1986 for Programs of Excellence for Research on Osteoporosis, soliciting projects of basic, clinical, epidemiological, or animal model investigations on osteoporosis.

Two independent studies of perimenopausal and early postmenopausal women suggest that bone loss, at least from the spine, may begin even before menses have ceased, possibly as early as age 35. Additional studies are required to understand the mechanism of action of estrogen therapy and whether it should be recommended for patients with osteoporosis or who are at high risk of developing the disease. To evaluate the benefits and risks of estrogen therapy, particularly the risk of cardiovascular disease in postmenopausal women, the NIA is collaborating with four other Institutes (NHLBI, NIAMS, NCI, and NICHD) to develop a major clinical trial.



*Productivity of the middle years can be extended and many disabilities of old age can be prevented, reversed, or postponed, thus improving the quality of life for older people.*

## Health and Effective Functioning

### *Health Attitudes and*

### *Health Behaviors*

Over half of the deaths in the United States are traceable to lifestyle and behavior. The NIA is concerned with research on everyday perceptions and the resulting frequent neglect of older people's symptoms, on self-care behavior, on the pertinence of risk factors to morbidity and mortality in the later years of life, and on the benefits of modifying health behaviors even at advanced ages. A program announcement issued in 1983, "Health Behaviors and Aging: Behavioral Geriatrics Research," emphasized the epidemiological linkages between social and behavioral risk factors and health outcomes, perceptions of and coping with aging and illness, and biopsychological linkages between health and behavior. Early findings of the subsequent work indicate that compared with young people, older people, as well as their physicians, are more likely to accept and "live with" symptoms rather than make efforts to diagnose, control, or alleviate them. Urinary incontinence goes widely untreated because it is mistakenly assumed to be an inevitable consequence of aging. Analysis of available data demonstrates that conformance with recommended health practices and lifestyle factors at older ages continue to be associated with decreased risks of mortality.

Further studies, longitudinal in nature and broadly representative, are needed to determine more explicitly the relation of psychological and social stresses and supports to health behaviors in older people, the lifetime development of adaptive responses, patterns of risk-taking behavior, and the reactions of older people to illness (including minimization of the significance of symptoms, delay in seeking medical care, and failure to comply with treatment and rehabilitation regimens). Gender differences in these variables and their outcomes must also be examined to help explain why women, though they tend to outlive men, evidence higher levels of morbidity.

### *Nutrition*

The goals of the NIA's nutrition program are to define the nutritional requirements for good health in older people; to determine if dietary deficiencies are associated with depressed immunocompetence, depressed cognitive function, deteriorated senses of taste and smell, or overt metabolic disease; and to understand how and why eating behaviors change with aging. NIA is preparing to solicit applications for Special Emphasis Research Career Awards for training and research support of studies of nutritional and metabolic factors in aging. In addition, NIA serves as the lead in a seven-Institute collaborative followup survey of the National Health and Nutrition Examination Survey I, which provides crucial information concerning the relationship between patterns of health and disease and specific nutritional status.

Subjects in the Baltimore Study described earlier are being examined for changes in bone density, body composition, plasma lipids, nutrient intake, and the control of blood sugar by insulin and other hormones. A previous BLSA study of dietary intake of male participants over three consecutive 5-year intervals provided the largest experience on nutritional practices across the adult age span. Recently dietary evaluations were reinstituted in men and initiated in women.

Analyses of BLSA data suggest that the relative importance of the fat distribution pattern and of total body fat as predictors of coronary risk factors varies with age. In middle aged and old men, fat distribution pattern was a better predictor of certain coronary risk factors (serum cholesterol, triglyceride concentration, and oral glucose tolerance) than was total body fat. Blood pressure level, on the other hand, was related more strongly to body weight than to the fat distribution pattern in these age groups. In very old men (over age 75), neither body fat nor its distribution is predictive of these risk factors. Future plans are to extend this work to include women, mortality, and the incidence of specific age-related diseases. Data show that the weights (adjusted for

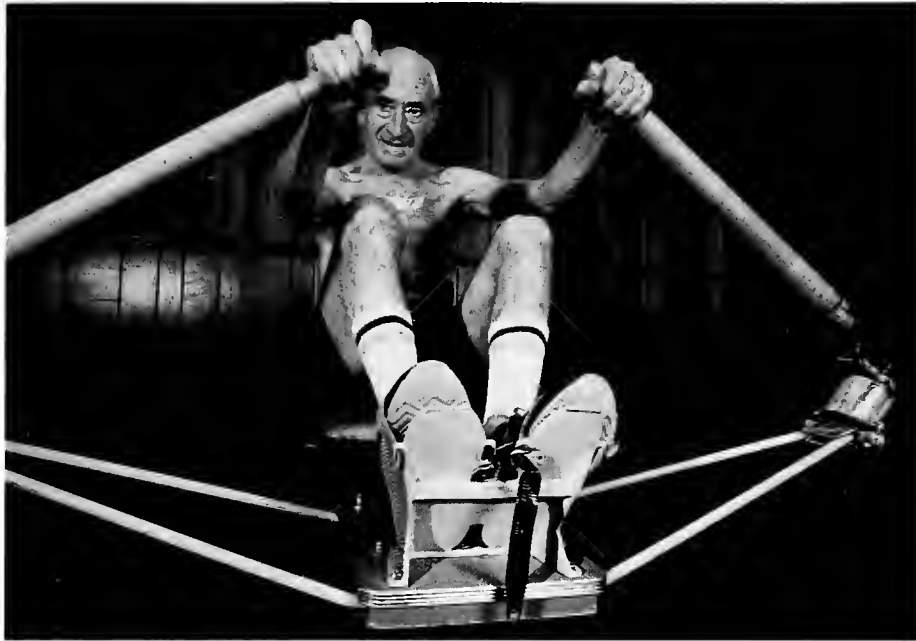
height) associated with minimum mortality increase with age; an age-specific height-weight table has been constructed based on these observations.

### *Exercise*

Research in exercise physiology is designed to assess the effects of both short- and long-term physical activity on the promotion of health (which includes the concept of rehabilitation) and on the prevention of premature physical decline and disease in older people. Of particular interest are adaptational responses of the nervous system, skeletal muscle, connective tissue, heart, blood and vasculature, and respiratory system. Approaches to exercise physiology range from studies of cell biology to studies of the whole organism, including not only classical *in vivo* research but also psychosocial studies of lifestyles and motivators fostering exercise, as well as epidemiologic studies.

The NIA recognized the need for research in exercise physiology and exercise medicine as related to aging processes and age-related diseases and disorders. In 1985 the Institute issued a program announcement for research projects to answer questions in this area. Does regular physical activity reduce the extent of or prevent age-related diseases and disorders? What criteria should be used to recommend exercise programs for healthy older people and for older people affected by various diseases? Studies in highly conditioned seniors show reduced metabolic risk factors for atherosclerosis and heightened cardiovascular function compared to their sedentary peers. Thus research is also needed to determine whether these changes are due to physical conditioning, lifestyle changes, or genetic factors.

NIA investigators have shown that, compared with young athletes, older athletes experienced only a moderate reduction in maximal aerobic exercise capacity. This was not the result of a reduction in either the maximal volume of blood pumped per heart beat (stroke volume) or the ability of tissue to utilize oxygen, but rather was



*Studies are being conducted to assess if and how regular physical activity reduces or prevents age-related diseases and disorders.*

primarily a function of the relatively small reduction in maximal heart rate which is a well known aging phenomenon. The implication of this is that regular participation in exercise programs prevents to a large extent the fall-off in physical working capacity that is commonly observed in sedentary older persons. Complementary to this, other studies demonstrate that previously inactive men and women with an average age of about 65 years improved their capacity for doing physical work in response to a long-term program of moderate-intensity physical training. This change was the result of a combination of favorable cardiovascular, pulmonary, and metabolic adaptations that appear still possible in the later years.

Another study indicates that walking or jogging three times a week increases bone mineral content of the axial skeleton in postmenopausal women. This appears to be the first report on the effect of exercise on the axial skeleton and is quite pertinent for understanding the role of regular exercise in preventing osteoporosis in women.

#### *Minority Health*

There has been tremendous progress in improving the health of the American population in general, but progress in improving the health and longevity of ethnic minorities has been less dramatic. There is a lack of scientific expertise focused on minority aging and an absence of broad interdisciplinary programs of research to provide this knowledge. In the spring of 1986, the NIA announced a program aimed at increasing the research support for studies in the field of minority health and aging.

In general, life expectancy, health status, and environmental influences are less favorable for nonwhite and ethnic minorities than for whites. The extent of the impact of the cultural changes on the lives of minorities has changed the baseline data on these groups. The impact of these changes on aging as well as on social and environmental strain and adaptation needs to be understood. The family structure, social networks, and problems associated with life transitions and their impact on aging of minorities need further research.

In September 1986, the NIA will sponsor a Conference on Research

on Aging Black Populations to initiate a dialogue between researchers studying the black population, enhance communications and networking between these researchers, and focus attention on the need for additional research in minority aging.

#### **Training and Career Development in Geriatrics and Aging Research**

The NIA supports a variety of training opportunities to help individuals prepare for or advance their careers in research and teaching in geriatrics and in biomedical, clinical, behavioral, and social science fields. In response to a 1984 congressional mandate requesting a Department of Health and Human Services (DHHS) plan of action to improve and expand training in geriatrics and aging research, a Public Health Service-wide task force was formed under the chairmanship of the NIA Director. The task force report, "Report on Education and Training in Geriatrics and Gerontology," documented the need for many more investigators and teachers. The plan calls for a doubling to tripling of postdoctoral fellows and trainees trained yearly in order to reach even the minimum number of faculty required in the Nation's medical, professional, and other graduate schools by the year 2000.

The NIA has designed several new mechanisms to help meet this challenge. The Geriatric Leadership Academic Award is designed to develop leadership and research and training activities in geriatrics at health centers and other health professional schools by supporting mid-level or senior faculty as academic leaders and program coordinators. The Complementary Training Award for Research on Aging permits strong, well-established research training programs in scientific fields relevant to aging to extend their efforts to individuals who are interested in careers in aging research. The Co-Funded Institutional National Research Service Award supports aging-related training positions on institutional training grants awarded by other NIH Institutes.

Since its establishment, the NIA intramural research program at the Gerontology Research Center in Baltimore, Maryland, has trained almost 400 individuals and is a major setting for postdoctoral training of promising young investigators (both M.D.'s and Ph.D.'s) for research careers in biomedical and behavioral sciences related to aging research and geriatrics.

Other NIA research and training efforts deserving special mention are the Special Emphasis Research Career Awards (SERCA) and the Teaching Nursing Home (TNH) Award. The SERCA supports scientists seeking careers in the study of nutritional and metabolic factors in aging and the study of behavioral geriatrics. The TNH supports research on clinical problems in nursing homes and other sites of long-term care for the elderly.

## Research Programs

The NIA conducts and supports research through four major programs: Biomedical Research and Clinical Medicine; Behavioral Sciences Research; Epidemiology, Demography, and Biometry Intramural Program; and the Intramural Laboratory Research Program. In addition to the research described in the section on High Priority Areas, progress in each of the four programs is presented below.

### Biomedical Research and Clinical Medicine

The Biomedical Research and Clinical Medicine (BRCM) program is responsible for: the planning, organization, and direction of programs of extramural research related to biological, clinical, and theoretical aspects of aging; the provision of basic biomedical and geriatric training; the conceptualization of new research directions and projects in the aging field; the management and evaluation of grant applications in relevant areas; and the dissemination of information to the scientific community, other Federal agencies, and the American public.

The NIA Animal Models program identifies and develops new animal models (mammalian and lower

organism) for use in aging research. Major objectives are to characterize new and existing models (longevity, pathology, relevance to human aging) and to supply animal and other biological resources to investigators in situations where NIA can produce these resources to higher quality standards and/or at lower cost. NIA, for instance, has established a reliable, stable supply of high quality, genetically defined rodents to satisfy the basic needs of a large portion of NIA grantees into the early 1990's.

In addition, the NIA has entered into an Interagency Agreement with the National Center for Toxicological Research, Jefferson, Arkansas, to breed and rear seven rodent genotypes for use in NIA-sponsored biomarker research. The addition of a new primate colony (the Delta Primate Center) will provide an alternative, large-mammal model resource. The development and characterization of animal resources is further promoted by the training of researchers with "gerontological awareness" and by providing well-characterized biological resource materials (animals, cultures, etc.) with which to conduct their research.

The Neuroscience of Aging program fosters research in the following areas: age-related changes or decrements in the structure and function of the nervous system, neural mechanisms of learning and memory disorders of the aged, including neurochemical and structural changes; age-related changes or impairments in sensory functions (e.g., auditory, visual, olfactory, and gustatory) as well as decrements in motor functions or fine motor coordination (e.g., hand-eye coordination); and neurological basis of sleep disorders, insomnia, and sleep apnea in the aged. The etiology, diagnosis, and treatment of Alzheimer disease and other dementias of the aged have already been described.

In studies on sleep apnea, at least one-third of a group of apparently healthy noncomplaining older persons show sleep-related respiratory disturbances. This borderline apnea

in disease-free, asymptomatic, aged people may indicate that this phenomenon is a common consequence of aging. Evidence also exists that mild to moderate, and often asymptomatic, sleep apnea may have a deleterious effect on cognitive function.

The Cardiovascular/Pulmonary/Renal (CPR) program focuses on: alterations in blood pressure regulation with age; isolated systolic hypertension; orthostatic hypotension; changes in the microcirculation; alterations in the composition of arteries and the effect of these alterations on cardiovascular function; changes in quality, quantity, and function of the myocardium and the conduction system of the heart; and changes in kidney and pulmonary functions.

The NIA, in conjunction with the National Heart, Lung, and Blood Institute (NHLBI), is cofunding a major clinical trial on the impact on stroke morbidity and mortality of treating isolated systolic hypertension (Systolic Hypertension in the Elderly or SHEP). Seventeen clinical centers and one coordinating center have been funded to recruit and treat 5,000 elderly persons in a double-masked randomized clinical trial.

NIA and NHLBI have issued a joint RFA on the mechanisms responsible for age-related changes in blood pressure. Both animal and human studies and wide varieties of scientific approaches are encouraged. Future plans include identifying processes that may be involved in stiffening, hypertrophy, and atherosclerosis of arteries.

The Endocrinology program encourages and supports research aimed at providing an understanding of the age-related changes in endocrine function, the mechanisms underlying these changes, and the impact of these changes on other physiologic systems.

The Genitourinary Disorders program supports and develops research on the epidemiology, pathophysiology, diagnosis, and therapy of urinary and fecal incontinence, prostatic hypertrophy, and impotence. A major developmental activity of the program has been the

continued coordination and monitoring of the clinical trials of behavioral therapies for urinary incontinence, cofunded by the Division of Nursing, Health Resources and Services Administration (HRSA).

A major epidemiological study of urinary incontinence in community-residing older people has found that the prevalence of incontinence is quite high, with 18.9 percent of men and 37.7 percent of women experiencing one or more episodes of involuntary urine loss in the prior 12 months. There were no important differences in the prevalence of incontinence by age.

The long-range goal of the Genitourinary Disorders program is to develop algorithms for the most parsimonious diagnostic procedures for patients with urinary incontinence and for the systematic application of treatment techniques (surgical, pharmacologic, behavioral, or combinations).

The Infectious Diseases, Hematology, and Oncology program supports research on the relationship between physiologic changes associated with age or chronic disease and susceptibility to infections, hematologic problems, and neoplasia. Other priorities include: evaluating vaccine efficacy in the elderly, new prophylactic techniques for infections in the elderly, age changes in the effects of chemotherapy, radiotherapy, and infection on granulopoiesis and lymphopoiesis, age-related changes in circulating levels of amyloid proteins and effects of amyloid deposition, and the interaction of aging and processes of carcinogenesis.

Studies on older persons' responses to the pneumococcal vaccine indicate that, although the antibody response tends to decline with age, the elderly are very heterogeneous in their responses. The percentage of persons with adequate antibody responses was not significantly different between community-residing elderly and young healthy subjects. However, a significantly higher percentage of institutionalized persons had inadequate responses. These findings indicate that chronic diseases of later life, rather than age per se, may be critical factors predisposing to infections.

The Immunology program supports and fosters basic research focused on cellular interactions to identify the loci of the immunological deficits observed in the aged and on the elucidation of the mechanisms underlying these impairments. The goals of these efforts are to be able to design prevention and/or treatment protocols which forestall or overcome any adverse effects resulting from age-related changes in immune functioning. In studies of immune function investigators have observed that key membrane structures on human B cells and monocytes, as well as T-cells, are altered in expression and in function with age. Normal cellular physiology of these regulatory networks are disrupted in certain elderly persons.

In studies of lymphocytes from young and old humans, it has been found that while comparable amounts of cytoplasmic factors controlling DNA synthetic activity are produced by the young and old lymphocytes, the nuclei from the old donors are significantly impaired in response as contrasted to those from the young donors. This impairment appears to be reflected as an increase in the response thresholds of the senescent immune system.

NIA encourages collaborative studies on aging between immunologists and neurobiologists. In 1985, NIA worked with the World Health Organization Working Group on Perspectives for Immunological and Neurobiological Research in Aging to encourage studies on brain-immune system interactions.

#### **Behavioral Sciences Research Program**

The NIA's Behavioral Sciences Research (BSR) program is concerned with research and training on those social and behavioral factors that affect both the process of growing old and the place of older people in society. The program provides leadership by working with other agencies both in the United States and abroad. The program draws upon many social and behavioral science disciplines and requires convergence with the biomedical sciences as well. The

long-range goal is to strengthen the social scientific basis for professional practice and public policy that can enhance the health and well-being of older people and can minimize the personal and social costs of health care and dependency. NIA provides the leadership for the NIH Working Group on Health and Behavior.

The program in Cognitive and Biopsychological Aging focuses on the mechanisms of age-related changes in intelligence, learning ability, memory, and sensorimotor functioning. Special attention has been given to Visual Perception and Human Factors approaches. Several projects have negated stereotypes of aging by showing that: macular pigmentation is not found to change systematically with age, no evidence of age-related brain impairment was observed in hypertensives, and the ability to manipulate images of objects in the workplace does not decline with age. There exists a potential for overcoming or ameliorating various age-related deficits: syntactic information can be used to minimize difficulties in interpreting rapid speech, written materials can be structured to facilitate memory of general ideas but not necessarily of details, and training regimens can reduce age-related deficits in intellectual functioning. Promising practical results include: an electrotactile sensory device worn across the abdomen which improves the hearing ability of deaf older people and tests that can predict impaired contrast sensitivity to such everyday targets as road signs and can measure decrements in the sense of smell which put older persons at risk of not being able to detect dangerous odors, such as gas leaks. Studies indicate that 45 percent of persons over 60 years old are unable to detect reliably the odor of commercial propane at realistic levels, as compared with 10 percent of persons under 40.

The Social Psychological Aging program encompasses two other major components of the NIA initiative on Health and Effective Functioning: (1) Behavioral Geriatrics Research, which focuses on changes



with aging in health-related behaviors and attitudes and their consequences; and (2) Productivity in the Middle and Later Years, which is concerned with strategies for optimizing human performance and independence throughout adulthood.

The program on Older People in Society is substantially involved in the NIA initiative on the Oldest Old. This program also supports a wide range of projects aimed at understanding the status, needs, and well-being of older persons. Projects range from investigations of the frail elderly and their caregivers to studies of migration patterns, cross-national expenditures for pensions, and new ways of analyzing multiple causes of mortality. Several illustrative findings can be mentioned. The number of centenarians in the United States is considerably smaller than estimated earlier by the Bureau of the Census, and methods of reporting at the older ages are currently being improved. Compared with many other developed countries, the United States has a high rate of poverty among the elderly. Older women living alone have levels of general health and functioning similar to those living with nonspouse others. The great bulk of care for frail older people comes from family members. Feelings of obligation to provide socioemotional and financial support to kin are strongest between parents and children, with strongest obligation toward unmarried or widowed kin.

#### **Epidemiology, Demography, and Biometry Intramural Program**

The primary focus of research and training in the Epidemiology, Demography, and Biometry program is gathering information on the health and functioning of noninstitutionalized, community-dwelling elderly, as well as the study of certain diseases and chronic conditions that are frequent health problems of the elderly (such as dementia, osteoporosis, heart failure, stroke, blindness, deafness, and physical disability), and known concerns to aged Americans (such as dry skin, pain, constipation, and all aspects of dying). Age-specific data are needed

since most of the data available from the census and from the National Center for Health Statistics have been inadequate.

Four community-based studies in a project entitled "Established Populations for Epidemiologic Studies of the Elderly" (EPESE) provide information on death, chronic conditions, disabilities, and institutionalization among representative samples of elderly persons living in communities. Preliminary results indicate that the three communities for which we now have data are very similar in some health characteristics (rates of cardiovascular disease) and quite different in other aspects of health (rates of physical and cognitive impairment). An interesting finding is that a surprisingly high proportion of the EPESE participants who were disabled when they were first interviewed have since improved, many regaining independence. The differences between those who improved and those whose physical functioning deteriorated are currently being studied.

The Epidemiologic Followup Study of the first National Health and Nutrition Examination Survey, a collaborative effort with the National Center for Health Statistics, provides cohort data on a large sample of the United States population. Analyses are currently under way to define what factors predict the later development of coronary heart disease, cancer, stroke, hip fracture, physical disability, and cognitive impairment.

The NIA Macroeconomic-Demographic Model, a complex mathematical, computerized description of relationships between economic, health, and demographic variables for the Nation, has been developed and is being used in a number of settings.

The "Survey of the Last Days of Life," a descriptive study of approximately 1,100 deaths sampled from among all deaths occurring over a period of 1 year in Fairfield County, Connecticut, is generating information concerning how elderly people die, the immediate circumstances surrounding their deaths, and

associated conditions existing at death approaches. The data collection phase is now nearing completion.

#### **Intramural Laboratory Research Program**

The major NIA intramural laboratory research program (IRP) which consists of seven laboratories is located at the Gerontology Research Center (GRC) within the Francis Scott Key Medical Center complex in Baltimore, Maryland; the intramural Laboratory of Neurosciences is housed at the NIH Clinical Center in Bethesda. In addition to its basic and clinical research program, the IRP is a major setting for postdoctoral training in biomedical and behavioral science related to aging research and geriatrics.

Research in the Laboratory of Neurosciences has shown that, in healthy subjects—where diseases such as diabetes and hypertension are not present—brain metabolism as measured by positron emission tomography (PET) does not decline with age. These results, which are in striking contrast to those from prior studies, provide definitive evidence that loss of brain functional activity is not a necessary consequence of aging.

The Laboratory of Molecular Genetics is investigating the molecular basis for aging and age-dependent diseases. The newly constituted Longitudinal Studies Branch is responsible for the central management and operation of the BLSA.

In the Laboratory of Behavioral Science (LBS), recent findings indicate that monkeys can learn to attenuate the increase in heart rate associated with exercise, and that this modulation seems to result in more efficient circulatory activity. Further research may lead to developing training procedures for patients with heart diseases which limit their capacity to exercise. Other LBS research suggests that there are significant diurnal variations in the regulation of the circulation which may have implications for improved methods of drug management of circulatory disorders during periods of sleep and waking. Laboratory scientists have also demonstrated the ef-



fectiveness of behavioral and biofeedback measures in controlling urinary incontinence in community-dwelling older persons. These studies are continuing with nursing home patients, in collaboration with the Health Care Financing Administration.

In the Laboratory of Biological Chemistry, research on the mechanism of action of parathyroid hormone in calcium absorption in the kidney has shown that the hormone stimulates a calcium-sodium transport system in cell membranes. This transport system is decreased in aging animals. Further investigations will focus on the development of bone and other cell type as experimental models to examine how hormones, including estrogens, parathyroid hormone, vitamin D metabolites, calcitonin, and glucocorticoids, act to regulate mineral deposition and loss.

In other studies, a unique pathway (calcium ion channel) which appears to have a primary role in controlling the rate of muscle response following electrical stimulation has been identified. Investigations of the processes involved in calcium ion reuptake that lead to relaxation of muscle have helped to establish the biochemical basis of age-related alterations in contractile activity. Additional research is needed to identify the cause of the diminished calcium ion uptake activity with age.

In the Laboratory of Cardiovascular Science, a collaborative study involving BLSA participants, discussed earlier, has provided extensive new information about the effect of age on cardiac structure and function during rest and exercise. Future plans are to determine the impact of chronic exercise on cardiac performance in elderly subjects; a proposed international study would determine whether specific age-related heart changes (vascular stiffness and left ventricular wall thickness and filling) within our "normal" range are in fact "normal" or whether they are absent in a population in which blood pressure does not increase with age.

In the Laboratory of Cellular and Molecular Biology, the participation of metal ions in genetic information transfer is being studied. DNA transcription occurs on the enzyme RNA polymerase, which has an initiation site on which transcription starts and an elongation site on which the RNA chain elongation is continued. Using metal ions bound to the initiation and elongation sites, the spatial relationship between the two sites has been partially worked out and, therefore, the structure of the active site of RNA polymerase. Nuclear magnetic resonance techniques are used to monitor the effect of age on cell and animal metabolism; these experiments are the only ones capable of determining *in vivo* how the rates of individual receptors in a complex series of biochemical processes are affected by aging.

Techniques of synthetic organic chemistry are used to expand understanding of hormone-mediated homeostasis in the aging organism. A new series of compounds has been developed which bind irreversibly to membrane receptors. When tested in experimental animals, they selectively deactivate receptors for particular classes of neurotransmitters—beta-adrenergic and alpha-adrenergic agents. These new probes are very promising tools for helping scientists understand the underlying neurochemical basis of various pathological states. Other research focuses on the development of chemical solubilizers which will increase the water solubility of liposoluble drugs, vitamins, and hormones, thereby facilitating their release and transfer to appropriate target tissues and organs.

In other studies it was found that the ability of the female sex hormone estradiol to stimulate release of the gonadotrophic hormone LH from isolated rat pituitary cells in culture decreases with age. Such age-associated deficits can be substantially reduced if sufficient calcium can be forced into aged cells with ionophores, compounds which facilitate calcium entry into cells.

Other studies are directed at both the role of conformational fluctuations in determining the function of proteins and how fluidity and

mobility changes within membranes alter cellular function during aging. Evidence has been found that conformational fluctuations within hemoglobin not only determine oxygen affinity but contribute to the cooperative release of oxygen.

In the Laboratory of Clinical Physiology, scientists are working to dissect away the effects of "secondary" processes such as inactivity, diet, body composition changes (lean body mass, obesity, and fat distribution pattern), diseases, and medications so that true biological aging processes can be understood. In other studies, normal fat cells have been successfully cultured and their biochemical characteristics are under intense study. This new cell type holds promise for research on aging and obesity.

In studies of immune function, the immunodeficiency associated with aging has been shown to be due in large part to a loss in T-cell function, which is associated with a loss in the secretion of growth factors and a loss in the ability to express receptors for growth factor. The defect is not due to accessory cell function but is resident in the T-cells themselves. The activity of the defective T-cells can be augmented by the addition of growth factors and accessory cells, and in some cases, the ability can be brought back to normal levels.

In the Laboratory of Personality and Cognition, evidence from the BLSA and national epidemiological studies continues to accumulate showing that personality does not change appreciably with age.

Analyses of data from about 10,000 respondents in a national survey showed no evidence for a midlife crisis or for personality differences with age. Investigators have contributed new insights about the stresses faced by aging adults, the methods and strategies used by them to cope, and the effectiveness of their coping efforts. Results from the BLSA reveal few significant age differences in coping mechanisms used to deal with stress. Further research is needed particularly on the personality dimensions of agreeableness and conscientiousness,

which are theoretically related to type A behavior and other constructs associated with coronary disease-prone behavior.

The longitudinal studies also indicate real but small diminution in performance on learning and memory tasks late in life in the absence of disease. The findings also demonstrate the wide range of individual variation in cognitive ability and function even in old age.

## Conclusion

In conclusion, while the NIA is only 11 years old, it has made substantial progress in promoting basic and clinical research on the biomedical, sociological, and behavioral aspects of aging. However, there are considerable challenges ahead. In setting the goals and objectives for the NIA to achieve its mission, on the bases of scientific readiness and societal needs, the following areas warrant further growth and support to the maximum extent feasible:

- Research on Alzheimer disease and related disorders including taking full advantage of the centers of excellence for research on Alzheimer disease.
- Research in molecular genetics and cell biology to investigate the mechanisms of aging.
- Research on the oldest old including developing procedures for forecasting the health status of this population.
- Accelerated recruitment of more women into the Baltimore Longitudinal Study of Aging to help determine the basis for sex differences in disease development and longevity.
- Research on osteoporosis through the development of programs and centers of excellence; after Alzheimer disease, osteoporosis is the second most important silent epidemic among older people, especially women.
- Emphasis on studies aimed at understanding how we can maintain health and effective functioning, including self-care, nutrition, exercise, and intergenerational relations both at family and societal levels.

- Support for training adequate numbers of teachers and investigators in geriatrics and aging research as provided in the DHHS report entitled "Report on Education and Training in Geriatrics and Gerontology."

## The Biennial Report of the Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

### History

The following events represent milestones in the development of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

- Major arthritis research programs were established at the National Institutes of Health in 1950 through the Omnibus Medical Research Act as a major component of the National Institute of Arthritis and Metabolic Diseases (NIAMD).

- 1972—(Public Law 92-305) the name of the Institute was changed to the National Institute of Arthritis, Metabolic and Digestive Diseases (NIAMDD).

- 1980—(Public Law 96-538) it became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

- 1985—The Health Research Extension Act of 1985 (Public Law 99-158) reestablished the programs of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases as two Institutes: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

- 1986—Dr. Lawrence E. Shulman was named Acting Director of the Institute.

### Introduction

Disorders such as arthritis, diseases of skeletal support structures, and diseases of the skin are among the most common causes of pain, disfigurement, and disability. In addition to the toll they exact in terms of human suffering, the economic impact of these disorders ranges into billions of dollars each year for medical care and lost productivity. Arthritis and related

diseases afflict nearly 37 million Americans.\* Arthritis is the Nation's primarycrippler, causing increasing numbers of people to leave the work force before normal retirement age. The resultant loss of earnings has been estimated at \$25 billion a year. Arthritis is reported to affect more than 40 percent of people over age



*An estimated 250,000 children have arthritis or joint disease. Many will carry serious handicaps into adulthood.*

65. An estimated 250,000 children have arthritis or a related joint disease; many of these children will carry serious handicaps into adulthood. Research efforts of the NIAMS, implemented through extramural research grants and contract programs, include investigations at major universities and medical schools throughout the country and abroad. Research in these disease areas also is conducted in the NIAMS intramural Arthritis and Rheumatism Branch and the Laboratory of Physical Biology at the NIH Clinical Center.

\* Source: National Commission on Arthritis and Related Musculoskeletal Diseases



*Osteoarthritis is a leading cause of pain and disability for older Americans, but technological improvements have set the stage for major advances in the next decade.*

## Research Focus—Arthritis

### Overview

The term "arthritis" (or rheumatic disease) encompasses more than 100 different disorders of the joints and connective tissues, including rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus (SLE), ankylosing spondylitis (spinal arthritis), and gout. Investigation into the area of arthritis, the original mandate of the NIAMD, has continued to receive significant research emphasis. The specific causes of many types of arthritis remain to be discovered. Considerable progress has been made, however, in our knowledge of several of these rheumatic diseases.

Advances in fundamental science are contributing to an increased understanding of disease processes and mechanisms at work in arthritis, including the role of infectious

agents as initiators, and immunologic and genetic factors in causation. Over the last three decades, these chronic, crippling disorders have yielded significant ground to research. Depending on the severity or degree of progression, many of these diseases can now be controlled with medications and other types of therapy.

### Research Programs

Research effort in arthritis can be assigned to three general areas: (1) projects associated with immune disturbances, autoimmune diseases, rheumatoid factors and other auto-antibodies, antigen-antibody reactions, and immune complex formation; (2) research concerned with collagen, connective tissue, basement membranes, synovial fluid, and articular cartilage; and (3) research projects in several specific rheumatic diseases (rheumatoid arthritis, degenerative joint diseases,

systemic lupus erythematosus, gout, and heritable disorders). Major avenues of specific arthritis research include humoral and cellular immune abnormalities in pathogenesis; mechanisms by which mediators of inflammation, such as the prostaglandins and leukotrienes, promote and regulate inflammatory reactions in arthritis; immunogenetic factors underlying susceptibility to arthritis; ultrastructure and pathophysiology of collagens, proteoglycans, and other components of connective tissue; and metabolic derangements underlying gout/pseudogout, osteoarthritis, and other diseases.

### Conferences

- A conference was held in New York City, October 17-19, 1985, under the auspices of the New York Academy of Sciences to discuss recent advances in collagen research. It was designed to present new developments in the rapidly changing area of biology of collagen, to acquaint physicians and biologists with this new information, and to promote close interactions between them.
- Support was provided for the Fifth International Symposium on Human Purine and Pyrimidine Metabolism, which met in San Diego, California, July 28-August 1, 1985. The objective of the conference was to emphasize new developments in the knowledge of human purine and pyrimidine metabolism at the basic level (biochemistry, enzymology, cell genetics, and pharmacology) and as it relates to a wide range of inherited and acquired diseases.
- A Conference on Epidemiology of the Rheumatic Diseases in the Americas was held in San Jose, Costa Rica, on July 6-11 1985. The purpose of the conference was to bring together epidemiologists, rheumatologists, and young investigators from the Americas to generate ideas and increase interactions for productive epidemiologic research in the rheumatic diseases.

### Program Plans

#### *Rheumatoid Arthritis: Research on Causes and Mechanisms*

Rheumatoid arthritis remains the major crippling disorder among the rheumatic diseases. Findings from research over the past few years make it more likely that rheumatoid arthritis is caused not solely by a single microorganism (virus, bacterium) or a deranged host factor, but rather by different agents generating immune responses that later lead to chronic inflammation in those with genetically determined immune regulation and biochemical abnormalities.

Many new basic research methodologies have been developed and are now available for finite experiments to test this and other hypotheses. These new technologies include monoclonal antibodies, recombinant DNA and molecular biology. In addition, new experimental animal models have been developed (e.g., rheumatoid arthritis with high-titre rheumatoid factor emerging spontaneously in MRL/l mice, or arthritis induced by immunization with type II collagen).

#### *Intensive Search for Infectious Agents in Early Arthritis*

In certain major rheumatic diseases of unknown etiology such as rheumatoid arthritis, systemic lupus erythematosus, and the spondyloarthropathies, there is current interest in several microorganisms as primary initiating factors in a possibly genetically determined immuno-compromised host. New biomedical research methodologies have been developed enhancing the potential for identifying such microorganisms or their products in tissues. At present, based on research in both animals and humans, there is special interest with respect to rheumatoid arthritis in mycoplasmas, Epstein-Barr virus, and parvovirus. In the spondyloarthritic group of rheumatic disease, candidate agents are salmonella, shigella, klebsiella, yersinia, and chlamydia.

Advice and guidance concerning the design and protocol for these studies have been obtained from a special scientific panel organized by

the National Arthritis Advisory Board from the Institute's Ad Hoc Arthritis Research Advisory Committee, and from a special task force convened to discuss the details, feasibility, and strategies for initiating and performing such studies. These groups were both encouraging and supportive of this research initiative. This program initiative will attempt to stimulate new activity utilizing modern advances in biotechnology to determine the role that infectious agents may play in the etiology of rheumatoid arthritis and other forms of inflammatory joint disease of unknown causes.

#### *Research Grants for Ankylosing Spondylitis and Related Spondyloarthropathies*

Diseases of interest include ankylosing spondylitis, Reiter's syndrome, arthritis of inflammatory bowel disease, psoriatic arthritis, and reactive arthritis.

The striking association between the genetic marker HLA-B27 and ankylosing spondylitis (95 percent) and related spondyloarthropathies, such as Reiter's syndrome (75 percent) was established 10 years ago; yet the mechanism by which HLA-B27 exerts its role in pathogenesis remains obscure.

A major recommendation of the Prevention Conference on Arthritis held in 1983 was an epidemiologic study to identify triggering agents, specifically a prospective cohort study in a high-risk group. This group would be composed of families of HLA-B27-positive spondylitic patients with a large sibship of adolescent males, residing in areas of high exposure to putative infectious agents.

Several research grants will be awarded under this initiative, with the intent to determine whether and if so, how, HLA-B27 or other related immunogenetic determinants predispose to spondylitic disease; to ascertain any role from gram-negative enteric or other organisms in triggering these diseases; and to determine reasons for predilection for these diseases in young men.

### *Workshop in Immunogenetics and Rheumatic Diseases*

Numerous advances have been made by rheumatologists in the areas of immunogenetics, immunopathology, and immunological expression of rheumatic disease in general. Understanding of the precise pathogenetic roles of immunological events in these disorders is still incomplete. A workshop will be planned in these areas to bring together investigators working on various aspects of these phenomena and to relate what is known in basic immunology, both cellular and humoral, to the pathophysiology of specific rheumatic diseases. The exchange of ideas will stimulate, promote, and give direction to research in these important areas.

### *Research Interest in Vascular Spasm and Scleroderma*

Scleroderma, or progressive systemic sclerosis, is a chronic disorder characterized by an attenuation of the microcirculation and diffuse fibrosis of the skin and internal organs.

Recently, several new agents with diverse specific pharmacologic actions have been reported as highly effective or promising in correcting the vascular pathology of scleroderma. Treatment with captopril, the inhibitor of the angiotensin-I-converting enzyme, has proven life-saving in scleroderma patients with malignant hypertension and early renal failure; digital ulcers have improved, perhaps from a bradykinin-like action of captopril. New calcium-channel-blocking agents, such as nifedipine, have been effective in combating Raynaud's phenomenon and scleroderma. In addition, there have been recent preliminary favorable reports of an antiserotonin agent, ketanserin, in treating Raynaud's phenomenon and scleroderma. With the help of basic research on the circulation and ascertaining the finite mechanism of action of these agents, there is promise of gaining understanding of the etiology of Raynaud's phenomenon. Thereafter, the relationships between the vascular pathology and connective tissue overgrowth may be better addressed.

Attention is being devoted to pathologic changes taking place in the smallest peripheral blood vessels, the microcirculation. Efforts will be made to stimulate research on disturbances of the microcirculation and pharmacological interventions in Raynaud's phenomenon and systemic sclerosis.

### *Establishment of Specialized Centers of Research in Arthritis and Musculoskeletal Diseases*

This new program of specialized centers of research (SCOR's) is being considered. Specialized centers of research provide a highly effective means of concentrating research efforts (in terms of personnel, resources and facilities) on selected high priority rheumatic diseases of national importance. Research efforts of the individual centers are multidisciplinary and consist of integrated programs with both a basic science and a clinical research emphasis, ensuring that advances in the basic sciences are rapidly translated into clinical applications and that clinical imperatives will provide direction for the basic science. SCOR's will provide a very valuable complement to the Division's portfolio of investigator-initiated research projects, not an alternative.

This initiative would start with SCOR programs in osteoarthritis, rheumatoid arthritis, and osteoporosis—each a major public health problem and a vital feature of the Secretary's initiative in arthritis—with a minimum of three SCOR's for each disease program. These specialized centers would conduct needed basic and clinical research in these important rheumatic diseases as recommended by the National Arthritis Advisory Board in its most recent Annual Report, and by the Institute's Advisory Council.

### **Special Programs**

The new Institute's programs are organized to be responsive to public health needs as well as to the areas of research opportunity and needs identified by working scientists in the academic community. In addition to that broad spectrum of research, the Institute supports a

network of arthritis centers, an Arthritis Information Clearinghouse, and an Arthritis Epidemiology and Data Systems Program. Multipurpose arthritis centers serve as major resources for generating new knowledge by fostering innovative research on the causes and control of arthritis and related musculoskeletal diseases. Centers also demonstrate and promote the application of this new knowledge for improved diagnosis and treatment of arthritis. The Arthritis Information Clearinghouse serves as a nationwide information broker for health professions; it is concerned with educational materials and programs available for professionals in their interaction with patients and their families and the public. The Arthritis Epidemiology and Data Systems Program serves as the administrative focus of efforts to encourage and support epidemiologic research in the fields of arthritis and related musculoskeletal diseases.

### *Arthritis Information Clearinghouse*

The need for an arthritis clearinghouse was identified by the National Arthritis Commission in its 1976 report to Congress; it was then authorized by Congress under P.L. 94-562. Established in September 1978, the Arthritis Information Clearinghouse (AIC) is fulfilling its major role as a catalyst to improve communication among health professionals who provide care and treatment for arthritis patients in the United States. The target audience for the clearinghouse includes physicians, nurses, physical therapists, occupational therapists, other allied health professionals, health educators, health planners and administrators, and medical librarians. Major functions of the clearinghouse are to identify, collect, screen, store, and disseminate information about educational materials and programs for the rheumatic diseases. In serving as a broker to foster the flow of arthritis information by helping users to locate education materials, the clearinghouse refers clients to the appropriate developer or source, rather than acting primarily as a distributor of the material itself. An 11-member advisory group composed of rheumatologists, educators,

library scientists, and allied health professionals assists the clearinghouse in the effective planning and accomplishment of its goals.

The clearinghouse consolidated its holdings in the National Combined Health Information Database (CHID). The CHID is the outgrowth of cooperative efforts by Public Health Service clearinghouses to make their individual data bases available to the public through a commercial data base vendor. The CHID became available to the public in January 1985 and contains more than 20,000 records. The AIC data base represents more than 4,000 records, and updates to reflect new materials are made regularly. A search reference guide was prepared by the AIC to assist users of CHID, and an updated and revised AIC thesaurus was made available to clearinghouse users.

A new type of publication for health professionals, the biblio-profile, is now available from the AIC. A biblio-profile is a brief, yet comprehensive state-of-the-art report, that provides an overview of a topic, indicates its current importance to the field, and points to areas where there is a need for additional information. The clearinghouse and its advisory group select the topics for this new series, and experts prepare them. To date, five biblio-profiles have been prepared.

**Epidemiology/Data Systems Program**  
The Epidemiology/Data Systems Program provides an administrative core for efforts to encourage epidemiologic research in the fields of arthritis and musculoskeletal diseases.

All data collection for the first National Health and Nutrition Examination Survey (NHANES I) Followup Survey was concluded in 1985, and the continuation of the followup by phone contact was implemented. The epidemiology staff of the NIADDK Division of Arthritis, Musculoskeletal, and Skin Diseases (AMSD) in collaboration with the staff of the National Institute on Aging and staff from other Institutes of NIH continued to refine the data tapes and carry out initial analyses.

The objectives of these studies are to: (1) identify chronic disease risk factors associated with morbidity and mortality; (2) ascertain changes in risk factors, morbidity, functional limitation, and institutionalization between NHANES I and subsequent recontacts; and (3) map the natural history of chronic diseases and functional impairment in an aging population. Osteoarthritis of weight-bearing joints is the subject of the first of such projects.

The Arthritis Data Systems Program fosters systematic acquisition, storage, retrieval, and analysis of information concerning rheumatic diseases. Attention is given to assuring validity, confidentiality, and comparability of data collected in separate institutions and to integrating data resources with data needs.

Rheumatic diseases data collection efforts and instrument development are carried out in three major settings: (1) the American Rheumatism Association Medical Information System (ARAMIS), (2) the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup, and (3) the arthritis centers.

The National Arthritis Data Work Group completed two journal papers on the best available prevalence figures for the major rheumatic diseases and the financial burden incurred. A third article has been outlined by the Work Group to assess the impact of disability related to the rheumatic diseases in the United States. The Data Work Group members have also gained in-depth knowledge of the data-gathering system at the National Center for Health Statistics, as well as the content of specific rheumatic disease items included within various surveys. This information is being used to provide advice to the National Center for Health Statistics in preparing new data items for the third National Health and Nutrition Examination Survey (NHANES III).

## **Cooperative Systematic Studies in the Rheumatic Diseases**

Research on the treatment of the natural history (evolution) of specific rheumatic diseases is one of the major objectives of the Arthritis Research Program of NIAMS. To meet this objective, a multi-centered organization has been developed and supported in recent years consisting of a Coordinating Center at the University of Utah and eight Participating Clinics, supplemented by collaborating clinics for special studies. The investigations performed by this program include expertly planned and conducted studies of new and promising drugs and controversial treatments, and natural history of disease. Well-designed systematic cooperative studies have produced important definitive information on the efficacy and safety of several anti-rheumatic drugs. Multi-centered control trials that have been completed recently or are in progress include:

- Low-dose methotrexate in refractory rheumatoid arthritis.
- Clinical and serologic evolution of early undifferentiated connective tissue disease.
- Sulfasalazine in rheumatoid arthritis.
- Post-marketing surveillance of methotrexate in rheumatoid arthritis.
- Comparison between analgesic and anti-rheumatic drugs in osteoarthritis.
- Anti-malarial drugs in early systemic lupus erythematosus.
- Combination of methotrexate plus oral gold versus oral gold in rheumatoid arthritis.

## **Highlights of Research Advances**

### *The Earliest Lesion in Rheumatoid Arthritis May Not Be Inflammation but Synovial Lining Cell Proliferation*

A mouse strain showing a spontaneous inflammatory arthritis and characteristic antibodies (rheumatoid factors) in its serum has been discovered to be an excellent model of rheumatoid arthritis—the MRL/l mouse. A comprehensive time-oriented study has unexpectedly indicated that inflammation is a late



manifestation of joint disease in this model; the early stage consists of proliferation of synovial lining cells. A striking feature is a dissociation between this cell proliferation and early joint destruction, and later on, overt inflammation. Further investigations are required to elucidate the mechanisms of human tissue injury involved. A search for one or more exogenous (environmental) triggering agents, such as a retrovirus, is required.

#### *Cellular Immune Responses in Lyme Arthritis*

Lyme arthritis, discovered just 10 years ago, begins with a characteristic spreading skin rash, erythema chronica migrans, followed then by an acute, intermittent or chronic arthritis in over half the patients. Some patients also develop nervous system or cardiac abnormalities. The illness is caused by a spirochetal bacteria, *Borrelia burgdorferi*, and is transmitted from deer and other hosts to man by ticks, *Ixodes dammini*, or other species. Its successful treatment with an antibiotic was described in the last Annual Report. Recent research on specific antigen-induced cellular immunity in Lyme disease has now shown that the responses of blood mononuclear cells to the *Borrelia burgdorferi* antigens increase as the disease progresses. Moreover, in those with arthritis, this cellular immune response to the causative bacterial antigen is greater in synovial fluid mononuclear cells from inflamed joints than in peripheral blood mononuclear cells.

*Total Lymphoid Irradiation for Intractable Rheumatoid Arthritis*  
Total lymphoid irradiation (TLI) is a technique of irradiation (x-ray) of each of the body's lymph node groups in sequence; it was originally developed to treat stage III Hodgkin's disease. It induces a long-lasting suppression of cellular immune responses (those regulated by T-cells), without evidence of increased risk of hematologic malignancies.

In a controlled trial, patients were randomly assigned to two treatment groups, a full immunosuppressive dose (2,000 rad) or a low dose (200 rad) TLI. These patients were those for whom previous drug and gold salt therapy had failed. Alleviation of arthritis disease activity was significantly greater in the high dose group, at both 3 and 6 months after radiotherapy.

The levels of serum autoantibodies (such as rheumatoid factor and antinuclear antibodies) did not fall with improvement in disease activity. This suggests that these autoantibody levels do not reflect disease activity of rheumatoid arthritis. Enthusiasm for this innovative therapy has been tempered by a significant number of serious complicating infections.

*Neuropsychiatric Manifestations of Systemic Lupus Erythematosus: A Possible Immunologic Basis*  
Central nervous system dysfunction (convulsions, organic psychoses) is a common occurrence in systemic lupus erythematosus; it is one of the serious life-threatening manifestations of the disease. Concepts of SLE as a disorder of immune regulation have been developing in parallel with the recognition and characterization of lymphocyte membrane reactive antibodies in lupus serum. Several studies have now documented a correlation between antilymphocyte antibody levels and disease activity in SLE, specifically with central nervous system manifestations of this disease.

It has been recently discovered that most lupus patients with neuropsychiatric manifestations have circulating antibodies reactive with neuronal cells of the human brain. Many of those antineuronal antibodies are cross-reactive with antigens on human lymphocytes.

#### *Anti-DNA Antibodies in SLE Can React With Antigens Other Than DNA*

The sera of patients with systemic lupus erythematosus contain antibodies that react with a variety of nuclear, cytoplasmic and cell-surface antigens. Lupus autoantibodies also lead to false-positive serologic tests

for syphilis by reacting with cardiolipin, a phospholipid. This anticardiolipin antibody in SLE is correlated with a circulating anticoagulant (which interferes with blood clotting). These serologic phenomena have been studied in mouse models of lupus by means of highly specific (monoclonal) autoantibodies produced (by the hybridoma technique) from the cells of inbred mice with the disease. This research revealed that a single antibody to DNA could react with many different synthetic compounds (polynucleotides). Some of the monoclonal antibodies to DNA cross-reacted with cardiolipin and other phospholipids.

Because such cross-reactions among these antibodies might have very important implications for understanding the stimuli for induction of antibodies to DNA in human SLE, hybridomas for the isolation of monoclonal human lupus autoantibodies were developed. A study of 30 monoclonal human lupus antibodies to DNA demonstrated that, as with the mouse lupus antibodies, many also react with other polynucleotides and, in some cases, with cardiolipin. The findings suggest that DNA itself need not be the only immunogenic stimulus for anti-DNA "autoantibody" formation in lupus. The antigen, for example, could be a phospholipid (such as cardiolipin) that could be an exogenous (environmental) antigen, rather than an autoantigen.

*A Predictive and Diagnostic Marker for Ankylosing Spondylitis*  
Ankylosing spondylitis (AS) is a chronic inflammatory disease of the joints in the vertebral column, manifested clinically by pain and progressive stiffening of the spine. It occurs primarily in young men. There is no "rheumatoid factor" antibody present in the serum (i.e., it is seronegative). It is frequently familial and its close association with one of the histocompatibility antigens (HLA-B27) suggests that genetically determined immune phenomena might contribute to this disorder. No serological abnormalities in AS have been uncovered.

A high incidence of antibodies directed against antigens found on chromosomes (taken from the fruit-fly, *Drosophila*) has been found in the blood of patients with ankylosing spondylitis. Moreover, the antibody was detected in AS patients even before all clinical parameters for a definite diagnosis became apparent.

Fluorescent staining of chromosomes provides a new serological marker in the sera of patients with AS and may aid in early diagnosis of AS.

## Research Focus— Musculoskeletal Diseases

### Overview

The Institute's Musculoskeletal Diseases Program supports basic and clinical studies on the several components of the musculoskeletal system in normal and diseased conditions. These include studies of the properties, growth, and metabolism of normal bone; bone and joint diseases, including metabolic bone diseases and inherited connective tissue diseases; musculoskeletal injury and repair; disorders of skeletal support structures such as tendons and ligaments; and specialized

studies in areas such as low back pain and locomotion. The increasingly important areas of exercise pathophysiology and sports medicine are other foci of this program. Research in joint replacement, bone and cartilage transplantation,



*Osteoporosis is a serious public health problem which affects millions of the elderly.*

and fracture healing has helped to restore mobility and freedom from pain for many Americans afflicted with diverse orthopedic conditions and diseases.

It is estimated that more than 40 million people are affected by these diseases, mainly from bone and joint disorders, fractures, and injuries of the tendons and ligaments.\* The resultant economic loss is enormous (estimated at over \$65 billion annually).

Significant advances in measuring bone density by noninvasive methods have enhanced our ability to diagnose and monitor many types of bone disease such as osteoporosis. These improved methods involve dual-photon absorptiometry, computerized tomography, and neutron activation.

Osteoporosis is receiving considerable attention and research support; it was the focus of a special NIH consensus development conference in 1984. Osteoporosis affects an estimated 15 million people in this country, including 90 percent of women and 45 percent of men over the age of 45. As the proportion of our population over 60 increases, osteoporosis and its related complications will be more evident and more costly if steps are not taken to prevent and treat this disease.

### Program Activities

The special programs discussed under the Arthritis research focus include activities for Musculoskeletal Diseases as well. In addition, the following events and accomplishments took place in this time period:

Among other skeletal diseases under investigation are osteogenesis imperfecta, a group of hereditary disorders which lead to fragile, easily fractured bones, and Paget's Disease, which affects 3 million Americans over the age of 40 with irregular bone formation and subsequent deformity.

\* American Academy of Orthopaedic Surgeons



NIAMS's Musculoskeletal Diseases Program supports studies of properties and growth of normal bone, bone and joint diseases, and musculoskeletal injury and repair.

## Workshops and Program Announcements

- *Molecular genetics in osteogenesis imperfecta: Program announcement.* A program announcement has been issued jointly by the Institute and the National Institute for Dental Research and has been broadly disseminated to encourage additional research on genetic lesions in osteogenesis imperfecta (OI), define specific defects in milder forms of OI, and promote initial efforts toward genetic counseling and therapeutic measures.

- *Pathophysiologic mechanisms in osteoarthritis: Workshop.* On July 21-25, 1985, a major workshop on the cause and pathogenesis of osteoarthritis was held to identify and focus future research approaches to osteoarthritis. Over 90 specific research recommendations generated at this conference will be published, and thus encourage studies on pathogenetic mechanisms in osteoarthritis, promote epidemiological research studies, and foster interdisciplinary investigations.

- *Origin and activity of osteoclasts: Workshop.* Osteoclasts are cells that resorb bone in a continuous remodeling process. The origin of these cells, attraction to the site of activity in bone, and mode of action have been the subject of much recent research.

A workshop on osteoclast function and Paget's disease was held at the National Institutes of Health in September 1985. This meeting defined recent advances and provided guidance for future research. A summarizing report of this successful workshop has been prepared for publication.

## Conferences

- A Gordon Conference on Bones and Teeth was supported by the Musculoskeletal Diseases Program once again this year. It met in Meriden, New Hampshire, July 14-19, 1985.

- A Gordon Conference on Biocompatibility and Biomaterials, held in Holderness, New Hampshire, on June 16-21, 1985, was also sponsored by the Institute.

## Program Plans

### *Osteoporosis: Clinical Treatment Studies With Estrogens and Progestins*

In April 1984, the NIADDK organized the Consensus Development Conference on Osteoporosis. This meeting described the current state of knowledge on causes and prevention of osteoporosis. One of the recommendations of the conference panel was to support "Studies to determine the optimal regimen of gonadal hormones for prevention of bone loss and fracture." In pursuit of that objective, a future program announcement will lead to the initiation of new studies to determine the appropriate doses and combinations of estrogens and progestins for prevention of osteoporosis. There is great need to evaluate risks and benefits of various combinations and doses of these hormones, their delivery schedules and delivery routes. The early studies will be a screening process to identify candidates for larger, more definitive, clinical trials.

### *Osteoporosis: Alterations in Bone Metabolism*

Another of the recommendations of the April 1984 Consensus Development Conference on Osteoporosis was to support "Studies to elucidate further the mechanisms of bone growth and remodeling, their local and systemic regulation, and their alteration in osteoporosis." Research applications will be encouraged to stimulate research addressing this recommendation to study changes in basic bone metabolism associated with osteoporosis.

### *Osteoporosis: Risk Factors for Hip and Colles' Fractures*

The April 1984 Consensus Development Conference on Osteoporosis also recommended the support of observational and epidemiological studies on the causes of this disease. Together with the National Institute on Aging, a request for applications will be designed to identify risk factors and predictors of fracture and bone loss in osteoporosis. A large prospective study is proposed to identify predictors of hip and wrist (Colles') fractures and to identify predictors of rapid bone

loss. The study cohort will be a subset of a recently initiated project on systemic hypertension in the elderly. Connecting the osteoporosis evaluation to a well-controlled existing study will be an economic method to include a very large cohort.

A longitudinal study of the occurrence and progression of osteoporosis is now under way in 200 women. The age of the population is such that fractures (and therefore risk factor data) are anticipated in the next 5-year grant period.

### *Research on Low Back Pain*

This coming year, a workshop dealing with low back pain will be scheduled. It is intended to assess recent progress in low back pain research and develop directions, encourage and support needed research on low back pain, and promote collaboration among scientists from different scientific backgrounds.

### *Exercise Pathophysiology and Sports Injuries*

This initiative is intended to promote fundamental studies in exercise pathophysiology (including research on muscles, tendons, and ligaments); interdisciplinary investigations; and epidemiological studies of sports injuries. A workshop in the spring 1982 served to stimulate interest. Additional support—new research projects, and a future center of excellence in this area—would focus attention and accelerate research progress.

### *Local Bone Regulating Factors*

A workshop on this topic was held at the NIH in the spring of 1983. Factors that regulate bone metabolism and remodeling were discussed in depth. Other factors that induce formation of bone in gap areas were described. Future clinical applications were identified. A program emphasizing work on local bone regulatory factors has been projected to foster research to extend major advances in bone cell regulatory factors, and to promote studies in clinical application of these new developments.

## Highlights of Research Advances

### *Osteoporosis: Age-Related and Menopausal Factors*

Postmenopausal bone loss (osteoporosis) is associated with an estimated 700,000 fractures each year in the United States. The relative contributions of the aging process itself and of estrogen deficiency to postmenopausal osteoporosis have been under debate, even though it had been known that estrogen replacement therapy begun soon after menopause or after surgical removal of the ovaries will impede bone loss.

To determine the degree to which estrogen deficiency alone or aging alone is responsible for postmenopausal bone loss, each member of a group of women whose ovaries had been surgically removed (oophorectomy) was matched for age and for years since menopause with two normal control individuals, one near the time of menopause (perimenopausal) and one postmenopausal, respectively. The density of bone mineral was determined by special radiologic techniques (absorptiometry). Results showed that the perimenopausal group, at the same average age as the oophorectomy group, had normal bone density; the other two groups had significant losses of bone density. The postmenopausal group, combining the effects of both age (20 years older) and lack of estrogens, had only slightly more bone loss than the oophorectomy group. It was estimated that in those patients, three-fourths or more of the bone loss was due to estrogen deficiency rather than aging. The rapid bone loss induced by menopause is assumed to be superimposed on a slower bone loss process related to aging. The latter is likely to be analogous to the process causing bone loss in older men.

### *Calcium Absorption Is Impaired When Stomach Acid Is Low*

Most calcium in food and dietary supplements is in a form that can be absorbed best when there is adequate acid in the stomach. The acid environment solubilizes the calcium. Older age groups and others with achlorhydria (lack of gastric acid

production) are known to have low blood calcium levels. The common form of supplement used for them is calcium carbonate, a relatively insoluble compound.

In a recent study of patients with achlorhydria, the absorption of calcium in carbonate form was significantly lower than in normal control subjects. Moreover, in the patients with achlorhydria, the calcium absorption from the carbonate form was significantly lower than calcium absorption in a soluble (citrate) form. In normal control subjects there was no difference in absorption between the two forms. These results were observed under conditions of fasting. When given with meals, the calcium carbonate was absorbed even by achlorhydric individuals, provided that the meal itself was acidic.

### *Relationship of Running to Osteoarthritis*

The cause of osteoarthritis, the most common form of arthritis, is unknown. Biomechanical stresses have been said to foster development and severity of osteoarthritis, and osteoarthritis is thought by many to be caused by "wear and tear" on joints. Investigators at an NIAMS arthritis center have conducted a prospective 5-year longitudinal case-controlled study to determine if and how running influences the development of osteoarthritis in older persons. There was no difference in symptom signs or joint space narrowing on x-ray between runners and nonrunners (matched controls). Running, therefore, was not associated with developing osteoarthritis.

### *Molecular Basis for Osteogenesis Imperfecta*

Osteogenesis imperfecta, the most common heritable disorder of connective tissue, has been found from previous studies to be a collection of clinically and biochemically distinct varieties.

Advances in understanding defects in molecular genetic coding for the synthesis of collagen, an important component of connective tissue, are based on the development of cloned

probes (cDNA probes) for segments and individual components of collagen chains. Recent research findings help to explain how serious clinical defects can result from small abnormalities in collagen and its precursor (procollagen) chains. Many defects were discovered near the carboxy (c-) terminal end of procollagen chains. Because collagen is assembled and twisted starting at the c-terminal end, most of the collagen produced can be grossly altered by the presence of relatively small defects at this end of the chain. Another finding was that, in a lethal variant of OI, one-half of the precursor procollagen alpha 1 chains were shortened. In assembling the triple helix with alpha 1 and 2 types of chains to make collagen, the defective components were irreversibly bound to the normal chains and in this way amplified the impact of the structural defects. Future research will likely identify additional point mutations that could be the origin of other less severe forms of OI.

### *Functional Role of Muscle Control in Scoliosis*

Scoliosis, lateral curvature of the spine, occurs in about 2 percent of the population (in females more than males). Many factors have been proposed to play a role in the etiology of scoliosis; to date no direct causal factors have been identified. Of considerable interest is a recent discovery that people with scoliosis have a central nervous system defect that makes them incapable of providing small corrective asymmetric muscle support to counteract minor anatomic imbalances. Early theories on scoliosis presumed that overactive muscle imbalances pulled the spine to one side, thus causing the curvature. These new findings support an alternative concept, that muscular control in patients with scoliosis lacks asymmetric-correcting ability.

### *Bone Growth Substances: A Key to Bone Health*

Bone is in a dynamic state of resorption and replacement that is normally in balance. Local factors help to control the deposition of bone and its continual flux. Technologic

breakthroughs, such as the ability to culture bone cells without serum and pure bone cell lines, have assisted in the isolation of new factors that locally regulate bone metabolism and turnover. Bone diseases, such as osteoporosis, may be caused by defects in such local factors.

A coupling factor that may explain the interconnection between resorption and rebuilding of bone has been recently discovered. Starting with a culture of pure osteoclasts (bone resorbing cells), a newly described protein was isolated and purified. This protein, termed human skeletal growth factor, induces an increase in DNA synthesis and growth rate in osteoblasts (bone producing cells) when introduced into cultures at low concentrations. Bone cells contain other local regulators of growth. From cultured skull tissue (calvariae), two bone-derived growth factors (BDGF) were produced. One factor, with a molecular weight of 30,000, stimulates mostly bone DNA synthesis; the other, with a lower molecular weight (10,000), primarily stimulates collagen synthesis. These functions are similar to those of other bone regulating substances such as platelet-derived growth factor (PDGF) and somatomedin-like peptides.

#### *New Cartilage for Worn and Diseased Joints*

A new approach for repair of diseased cartilage caused by osteoarthritis and other diseases is now being developed in a rabbit model. Autografts (thin shell-like portions of the same individual's cartilage from ribs) are placed in a cavity formed when defective cartilage segments are removed surgically. Early tests carried out at 3 and 6 months after grafting show approximately 60 percent biological acceptance. Early failures have been traced to biomechanical stability. Because these are autografts, there are no problems of biocompatibility. Two new approaches are surgical protection of the thin graft shell, with a net of dacron as a supporting device, and a post-surgical procedure employing continuous passive motion. Human experiments may be possible in the next 3 to 5 years.

#### *Functional Roles for Osteocalcin*

Osteocalcin (also called a bone Gla protein) is the most abundant non-collagenous protein in bone. Despite the identification of osteocalcin nearly 10 years ago and its prevalence in bone, a physiological role for osteocalcin is not yet identified. One proposed role for osteocalcin is as a chemical attractant for bone resorbing (osteoclast) activity. Osteocalcin depends on vitamin K, and scientists produced an osteocalcin-deficient rat model by treating mothers and pups with the anticoagulant, warfarin, a vitamin K antagonist. Bone particles from this model and from normal control animals were placed into muscle flaps of normal animals. Compared to bone from the control animals, bone chips from the osteocalcin-deficient animals were resorbed significantly less by the test animals. This is consistent with earlier findings that Gla is a chemoattractant for monocytes necessary for normal bone resorption. This osteocalcin-deficient model was also used to study growth plate development and mineralization. In one set of experiments, the warfarin-treated animals produced excessive mineralization and early closure of the growth plate. These results imply that osteocalcin may promote a slow and controlled rate of mineralization.

### **Research Focus—Muscle Biology**

#### **Overview**

The NIAMS research program supports a strong portfolio of investigations in muscle biology. Research in muscle biology is associated with the structure, function, contraction, metabolism, development, and regeneration of skeletal muscle, and work on certain muscle diseases—such as myotonia, dystrophies, and other myopathies.

#### **Conferences**

- A major conference on the "Molecular Biology of Muscle Development" was conducted March 15-22, 1985, in Los Angeles, California, under the auspices of the UCLA Symposia on Molecular and Cellular Biology.

- A Gordon Research Conference on "Muscle: Excitation-Contraction Coupling" was held July 29-August 2, 1985, in Tilden, New Hampshire. Support was provided by the Institute with two other NIH Institutes. This conference focused on molecular aspects of coupling between excitation and contraction, rather than on the electrical properties of the membrane impulse.

#### **Program Plans**

##### *Enhancement of Biophysical Techniques to Study*

##### *Molecular Mechanisms of Muscle Contraction*

Research proposals will be sought as part of an effort to characterize contractile protein structure better, and to visualize molecular changes producing contraction of muscle.

##### *Molecular Biology of Skeletal Muscle and Its Diseases*

This effort is to encourage new work that will enable us to understand better the molecular basis of muscle development and genetic diseases, and treat or prevent muscle diseases resulting from genetic or transcriptional abnormalities (those in the reading of the genetic message). The Institute has recently expressed its interest in this area through the support of a conference on Molecular Biology of Muscle Development.

Certain muscle diseases, such as Duchenne muscular dystrophy (DMD) and malignant hyperthermia, have specifically genetic causes. Understanding the mechanism of control may enable us to prevent expression of a defective gene product. Examples of faulty genetic expression are known to occur in muscle fibers affected by myotonic dystrophy, where there is a demonstration of unusually high levels of promiscuous expression, and in avian muscular dystrophy, where the neonatal myosin heavy chain is abnormally expressed in adult muscle.

#### **Highlights of Research Advances**

##### *Muscle Performance and Biology*

New efforts are being directed towards responses of muscle to exercise and physical training. Knowledge gained from basic studies of muscle physiology may contribute to



the design of more efficient training programs for athletes and others interested in promoting musculoskeletal fitness and developing optimal rehabilitation programs.

Muscles enlarge as the result of weight lifting. A long-held concept is that muscle fiber splitting, with subsequent increase in the number of fibers, is the primary mechanism of muscle enlargement. This appears to have been disproven. Institute-supported research has shown that the number of muscle fibers is established early in skeletal maturation and remains relatively constant thereafter. Hypertrophy (enlargement) of individual muscle fibers appears to be the mechanism for increasing muscle size.

Muscle performance is determined by the rate of metabolism, or oxidative status (low or high), and the twitch speed (fast or slow) of a particular muscle. In general, exercise produces the functional advantage of delaying fatigue and sustaining the supply of energy. Muscle fatigue and its recovery vary in different types of muscles. Slow muscle recovers from fatigue in less than 1 minute, whereas fast muscles require approximately 1 hour to recover. Recent experiments found that overloaded fast muscles convert to slow fibers, whereas immobilized muscles composed predominantly of slow-twitch fibers take on properties characteristic of fast-twitch muscles. New techniques of molecular genetics indicate that these physiological changes are based on shifts in the representation of specific proteins within muscle.

#### *Phosphate Metabolism in Living Muscle*

Metabolism of phosphate-containing compounds is central to muscle function. The direct energy source for muscle contraction is the breakdown of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and inorganic phosphate (Pi). Nuclear magnetic resonance spectroscopy (NMR) allows noninvasive studies of phosphate compounds in muscle at various activity levels or in disease states.

Mammalian muscle consists of three fiber types; these have substantially different metabolic responses to muscle stimulation. A recent NMR study compared two preparations: one was a slow muscle (soleus); the second a fast muscle of mixed fiber type (biceps brachii). There was a significant difference in the relative concentration of inorganic phosphate (Pi) in the two muscles at rest. This difference is more pronounced than that determined by traditional chemical analysis. The NMR results, being noninvasive and nondegradative, are likely to be more accurate. The Pi difference is of great interest because other studies show that the buildup of Pi is related to muscle fatigue. The low Pi level in resting fast muscles means that the relative Pi increase during contraction is magnified. This is consistent with the notion that Pi is an important regulator of ATP reformation by glycolysis and glycogenolysis in fast muscles, but not important in slow muscle, where an alternative pathway, oxidative phosphorylation, is the main energy source for ATP regeneration.

#### *Regulation of Contractile Activity*

Resting skeletal muscle is a primed engine, ready to produce force at a moment's notice. Force regulation is crucial to muscle function. A key to this regulation is control of the interaction of actin and myosin, the proteins which produce muscle tension. In many muscles the major control is through proteins bound to actin, which together form thin filaments. Certain types of muscle, however, have a control that is part of the myosin-containing thick filaments. Myosin molecules isolated from scallop muscle contain two light chains shown to have a regulatory effect and two light chains essential for activity.

Experiments using chemical cross-linkers show that the two regulatory light chains (R-LC) within each myosin molecule are closer than 9

angstroms for much of their length. The addition of calcium, which activates muscle, does not alter this. The major biochemical change appears to be at the other end of each R-LC, where it overlaps an essential light chain (SH-LC), and reaches out on the projection that includes the actin binding site. Structural studies of myosin filaments demonstrate considerable difference in the array of these projections depending on the presence or absence of calcium ions. The projections from individual myosin molecules form a smooth, orderly helical array on each filament in the relaxed state. When calcium is added, this array becomes disordered and rough. When calcium is removed, the filaments revert to the more ordered array. Together, these results indicate that the R-LCs and SH-LCs maintain myosin in an ordered array in relaxed thick filaments. Activation with calcium causes a movement of the SH-LCs relative to the R-LCs, resulting in a disordered filament, which in turn promotes interaction with actin filaments and the development of force.

#### *Control of Energy Metabolism in Muscle*

The mechanisms by which nerves control metabolic properties of skeletal muscle are unknown. Researchers have studied a tissue culture system of muscle cells arranged in tubules to investigate the influence of muscle activity on metabolic levels in the absence of nerves. Findings support the hypothesis that enzyme levels in muscle are controlled directly by the contractile activity of the muscle, rather than by a direct effect of nerves. Calcium ion appears to mediate these effects. Thus, regulation exercised by nerve is indirect, resulting from the stimulation of muscle twitches and spasms (tetany). This may be important in understanding certain muscle diseases; it may be possible to determine whether a particular muscle disorder is due to faulty neural control or some intrinsic defect in the response of the muscle to that control.



## Research Focus—Skin Diseases

### Overview

The Institute's Skin Diseases Program continues to support studies of both normal and diseased skin to obtain a better understanding of cutaneous diseases. The vast group of skin diseases causes a great deal of human suffering through discomfort, disfigurement, or chronic disability. Skin diseases are a leading cause of industrial disability. The medical, psychosocial, and economic costs of cutaneous disease justify an extensive and diverse research effort.

Areas of emphasis in the Skin Diseases Research Program include psoriasis and other disorders of keratinization; vitiligo and other disorders of pigmentation; photobiology, photoallergy, and phototoxic reactions; metabolic studies of skin, including effects of hormones and interaction with enzymes; immunologically mediated cutaneous disorders, including atopic dermatitis, eczema, contact dermatitis, and vasculitides; bullous diseases of the skin, including pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa; acne and physiologic activity of the sebaceous gland; disorders of hair growth, including alopecia areata; and cutaneous manifestations of connective tissue disease disorders, including lupus erythematosus, scleroderma, and pseudoxanthoma elasticum.

Over 60 million Americans have a skin condition that warrants a visit to a physician for treatment. Many of these diseases, such as acne, psoriasis, and eczematous and immunologic skin diseases are treatable in varying degrees at present; however, the etiology, means of prevention, and cure for most of them are unknown.

Research supported by the Institute is discovering that some forms of these disorders are caused by the abnormal production of a specific enzyme or an abnormal immune response of the body with the generation of antibodies reacting against one's own tissues (autoantibodies).

Investigations on the basement membrane zone of the skin are pro-

viding insights to the causes of epidermolysis bullosa (EB), a rare but serious skin disease with multiple genetic types and at least one acquired immunologic form. Some of the 35,000 people with EB suffer severely from this disease, including crippling and malnutrition. There appear to be several forms of this disease. Institute grantees are working to develop diagnostic tests for bullous skin disorders using monoclonal (highly specific) antibody technology, and to develop effective treatments for these diseases.

Past efforts have resulted in significant advances in the treatment of selected skin diseases, and there is hope for even greater advancement toward alleviating the damaging effects of such disorders.

### Program Activities

#### *Survey of Research Needs in Dermatology: An Update*

This comprehensive effort brought together a group of leaders in the field of dermatologic research to evaluate research accomplishments and delineate new areas of research opportunities that have developed since the publication in 1979 of the classic report "Analysis of Research Needs and Priorities in Dermatology."

Recognizing the need for an update to this analysis, Congress mandated that the NIADDK support such an effort during fiscal year 1983. Accordingly, a workshop was organized then and preliminary data gathering completed. This update on research was published in November 1984 as a supplement to the *Journal of the American Academy of Dermatology*.

#### *Dermatology Data Work Group*

A new National Skin Diseases Workgroup is being organized to focus on collecting data and reporting national estimates of major skin diseases for which such data are available and projecting estimates from defined population studies to supplement these statistics. In addition, the group will assess previously collected national data and prepare recommendations for NHANES III.

### Conferences

- A Gordon Conference on "Epithelial Differentiation and Keratinization" was sponsored and supported by the Institute on August 5-9, 1985, at Tilden, New Hampshire.

- The Institute contributed significant support to the 34th Annual Symposium on the Biology of Skin, on the subject of "Cutaneous Immunobiology," held at Gleneden Beach, Oregon, October 6-10, 1985. The proceedings of this symposium were published in the July 1985 issue of the *Journal of Investigative Dermatology*.

- A conference on Non-Dermatological Complications of Epidermolysis Bullosa is scheduled for September 8-9, of 1986, in Bethesda, Maryland.

### Program Plans

#### *Epidermolysis Bullosa Registry*

Epidermolysis bullosa (EB) is a group of heritable diseases in which skin and other epithelial surfaces, including the mucus membrane of gastrointestinal and respiratory tracts, form blisters and become denuded after physical trauma. As many as 20 possibly genetically distinct forms of EB have been described; some are often fatal early in childhood or are severely disabling. Recent advances have provided an impetus to further research in epidermolysis bullosa.

The epidermolysis bullosa registry will develop (by contract) a roster of well-characterized patients with different forms of epidermolysis bullosa willing to contribute specimens and to be followed as part of research protocols, to develop a registry of patients with this disease to obtain appropriate genetic and epidemiologic data concerning the various forms of the disease; and to determine the natural history and value of various therapeutic interventions in the different forms of epidermolysis bullosa, by following selected groups of patients.

#### *Animal Models of Skin Diseases*

A conference is being encouraged to bring together research workers with various scientific backgrounds to discuss: (1) naturally occurring

animal diseases that are the counterparts of human diseases; (2) induction of diseases in animals as models of human skin disease; and (3) transplantation to immunologically deficient animal hosts of human diseased skin, and mechanisms by which such transplanted skin can be induced to maintain its abnormalities. This workshop would assemble scientists working on human diseases for which animal models are lacking, scientists working with established animal models, and scientists in veterinary medicine.

#### *Mechanisms of Allergic and Irritant Contact Dermatitis*

Inflammatory processes, mechanisms of sensitization, and expression of delayed hypersensitivity are important in many cutaneous diseases. Occupational skin diseases, which are predominantly irritant in nature, comprise the largest single cause of industrial and occupational disease and accordingly, have a very large economic impact nationally. The initiative would take the form of a program announcement to emphasize interest of the Institute (along with two other Institutes) in these research areas.

#### *Pathophysiology of Effects of Retinoids*

Retinoids are a highly promising group of agents that have received widespread attention and use in Europe, and widespread attention but less use in the United States. They have been released by the Food and Drug Administration for treatment of severe cystic acne. Studies in Europe have indicated that retinoids are useful in psoriasis, and in certain keratinizing disorders. According to individual case reports, retinoids may also be useful in other diseases, such as lupus erythematosus. A program announcement to underscore interest of the Institute in this important area is planned in an effort to facilitate identification of biochemical and pathophysiologic mechanisms by which retinoids are therapeutically effective in severe acne and keratinizing disorders.

#### **Highlights of Research Advances**

##### *Epidermolysis Bullosa: Skin Defects That Help Explain Normal Skin as Well as the Disease*

Epidermolysis bullosa is a group of heritable diseases in which skin and other epithelial surfaces, including the mucous membrane of gastrointestinal and respiratory tracts, form blisters and become denuded after physical trauma. As many as 20 possibly genetically distinct forms of EB have been described; some are often fatal early in childhood or are severely disabling. The defects in all forms of the disease are within the skin's basement membrane zone; they provide a model system by which normal as well as abnormal structure and function in this area can be investigated.

Collagenase, the enzyme that degrades collagen, has been found to be increased in several forms of EB. The gene for collagenase has recently been cloned, promising further advances on the structure of the normal gene and the enzyme, and abnormalities in its structure and function in different forms of EB.

A drug that inhibits collagenase, diphenylhydantoin (trade name: Dilantin) has proven successful in ameliorating the disease in some patients with inherited recessive dystrophic EB.

There is one acquired immunologic form of EB. The protein to which antibodies attach in this one form has been identified, and partially purified. Such work will foster comparison between the immunologic acquired form of EB and its various hereditary forms.

The availability of several specific (monoclonal) antibodies to different constituents of the basement membrane zone has permitted the development of diagnostic (immunofluorescent) techniques that are faster and less expensive than electron microscopy, and has accelerated the diagnosis of EB patients.

Anchoring fibrils, structures in the upper portion of the dermis that have been discovered to be a key component in the attachment of epidermis to dermis, and found to

be defective in a severe form of EB, have been recently identified as being composed of type VII collagen.

##### *Pemphigus—New Clues to the Disease Process*

Pemphigus vulgaris is a severe blistering disease of the skin's epidermis and the mucous membranes. Circulating antibodies to epidermis in pemphigus were discovered 20 years ago. Recent research has demonstrated conclusively that these antibodies in human pemphigus are capable of reproducing the disease in an animal model (newborn mice).

Several groups have demonstrated that pemphigus autoantibodies can bind to the desmosomes (intercellular bridges) of the epithelium, the covering of internal and external surfaces of the body. Because desmosomes are thought to be the most secure attachment point between epithelial cells, this localization would seem to have pathologic significance. Yet other workers, utilizing injections of pemphigus autoantibodies into newborn mice, have demonstrated that earliest separation takes place between desmosomes and that desmosomal attachments are the last to split. Resolution of this dilemma is needed.

##### *Vitiligo: Immunologic or Toxic Origin?*

Vitiligo, characterized by white patches of skin, is a poorly understood disease that affects approximately 500,000 Americans. It is most notable and disturbing in darkly pigmented persons and may cause severe disfigurement and serious psychological stress. Mechanisms by which pigment cells (melanocytes) are adversely affected have been under active investigation for many years, with major emphasis on autoimmune destruction of melanocytes (destruction by the patient's own immune system). After many years of searching, a high incidence of autoantibodies to a melanocyte-associated antigen has been found in most forms of vitiligo.

Again, after many years of research, two animal models for vitiligo have been developed. The

first is a model in which the immune system of chickens can be manipulated before the development of vitiligo; these immunologic manipulations have been shown to delay the development of vitiligo. Endocrine manipulation can also affect the expression of vitiligo in this bird model. A mouse model for vitiligo has also been described recently.

A new hypothesis states that damage to melanocytes by some toxic substance causes the lesions in vitiligo, and that autoimmune abnormalities may be secondary, rather than being pathogenetically significant.

#### *Ichthyosis: Lipid Abnormalities May Be the Key Finding*

Ichthyoses, scaling diseases, are a group of both genetically inherited and sporadically occurring diseases characterized by excess accumulation of the cornified outer layer of the skin (stratum corneum). Recently, it has become clear that, in some forms of ichthyosis, significant abnormalities take place in the lipids that form the glue of the stratum corneum. In recessive X-linked ichthyosis, the defect in lipid metabolism seems to be an inability to remove sulfate from cholesterol sulfate in the stratum corneum. This engenders an excessive accumulation of scales of stratum corneum in this disease. In congenital nonbullous ichthyosiform erythroderma, another form of hereditary ichthyosis, researchers have discovered that the abnormality is in another type of lipid (derived from the N-alkanes). A third hereditary disease (with ichthyosis as part of a multisystem disease), the Chanarin-Dorfman syndrome, has been shown to have a defect in neutral lipid metabolism.

These lipid abnormalities, demonstrable in various forms of ichthyosis, point to the importance of stratum corneum glue in the development of ichthyosis. They also provide new insights for developing specific therapeutic attacks on these scaling diseases.

#### *The Skin as an Immunologic Organ*

It has been shown in recent years that the skin is an active immunologic organ rather than a passive bystander in immunologic reactions.

The Langerhans cell, a specialized cell in the epidermis, has been shown to be a primary cell involved in sensitizing the skin to foreign antigens. This sensitization involves both local antigen presentation in the skin, and transport of the antigen to the draining lymph node. In the skin, the processing of antigen by Langerhans cells results in the initiation of an inflammatory process. At the lymph node, the Langerhans cell processing results in suppression of the reaction. This dual function allows for both the initiation and the later suppression of the allergic reaction to a foreign antigen.

The presence of an immune response antigen (Ia) on the surface of cells is intimately involved in the presentation of antigen. Normally, Ia is not present on the surface of epithelial cells called keratinocytes. During active inflammation, however, epithelial keratinocytes do express Ia; this allows for amplification of normal presentation of antigen in allergic skin reactions.

In mouse models cells with markers specific for T-lymphocytes (a subset of white blood cells called THY-1 cells) act as antigen-presenting cells. This occurs, however, only centrally at the local draining lymph node rather than peripherally in the epidermis. This action serves to inhibit or "down regulate" the allergic immune process. An active search for THY-1 equivalent cells in human skin is ongoing.

The actions of Langerhans cells, THY-1 cells, and Ia-bearing epithelial keratinocytes explain both the sequential turning on of an allergic inflammatory response following exposure to foreign antigen such as poison ivy, and the later down regulation that turns off the allergic reaction. The ability to isolate different aspects of this sequence is allowing more detailed investigation of the mechanisms of action of specific agents, such as ultraviolet light exposure, topical and systemic corticosteroid administration, and other anti-inflammatory agents. Increased knowledge of specific events in allergic sensitization and

reactions will foster better design of protective maneuvers to minimize contact dermatitis; this is a major cause of skin disease generally and the single greatest cause of occupational disease.

#### *Skin Pharmacology: New Drugs and New Delivery Systems*

The stratum corneum of skin is an obstructive barrier to the delivery of biologically active drugs to deeper levels of the skin. Research in this area has led to advances in both drug design and drug delivery through the stratum corneum. A compound related to vitamin A (13-cis-retinoic acid) has been shown to be effective in treating severe cystic acne when administered by mouth; however, it does have many toxicities. Recent advances in the biochemical pharmacology of this group of drugs (retinoids) has resulted in the development of several substituted derivatives that are promising when applied topically. The new derivatives are designed to both penetrate the stratum corneum and be biologically active within the dermis and epidermis.

Psoriasis is a potentially severe skin disease that affects more than 1 percent of the American population. There are a number of effective therapies for severe psoriasis, including systemically administered cancer chemotherapeutic agents, such as methotrexate. Recent chemical advances have developed derivatives of these chemotherapeutic agents that can penetrate the stratum corneum and remain biologically active in the epithelial tissue. Their effects would ameliorate psoriasis but avoid the systemic side effects of orally administered chemotherapeutic drugs.

# National Institute of Arthritis and Musculoskeletal and Skin Diseases Tenth Annual Report on Evaluation of Multipurpose Arthritis Centers

## Overview

Multipurpose Arthritis Centers, previously a component of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, will be continued in the programs of the newly-enacted National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The centers were initiated in fiscal year 1977 in response to both the National Arthritis Act of 1974 (P.L. 93-640, Section 439), which first authorized a new, national program of comprehensive arthritis centers, and to the National Commission of Arthritis and Related Musculoskeletal Diseases which included 20 specific recommendations for centers in its long-range Arthritis Plan of 1976. The NIAMS Multipurpose Arthritis Centers are designed: (1) to foster and stimulate the prompt and effective application of available knowledge for the treatment of patients with arthritis and related musculoskeletal diseases; and (2) to develop new knowledge essential for the control of these disorders.

To this end, the centers are expected to develop and effect research programs in basic and/or clinical research; professional, patient, and public education; and community-related projects and health services research. A goal of the NIAMS is to encourage each center to achieve an optimal program balance, and also develop special innovative projects in one or more fields. This report will concentrate primarily on highlighting some examples of studies conducted during the past year which are reflective of the diversity of the programs in the centers.

## Center Biomedical Research Projects

Inherent in the concept of a Multipurpose Arthritis Center is a strong research component. Center grant support for biomedical research is intended to complement traditional research grant support in a given institution, to establish related special projects, and to stimulate development of new projects. Each Multipurpose Arthritis Center is expected to have ongoing research programs in basic and/or clinical biomedical research related to rheumatic diseases as a prerequisite for a center grant award.

Biomedical research projects supported by center grant funds are developmental and feasibility studies designed to encourage investigators to explore interdisciplinary and highly innovative scientific approaches which may later form the basis of applications for research grant awards from the National Institutes of Health or other agencies.

Biomedical developmental research projects in the Centers are varied and unique; examples include:

- An investigation conducted at the University of California Center in San Francisco, of molecular mechanisms responsible for the lack of expression of histocompatibility antigens in children suffering from the bare lymphocyte syndrome.
- A project at the Indiana University Center, to determine whether there may be changes in collagen cross-linking in joint tissues other than cartilage.
- A study at the University of Texas center in San Antonio, to determine genetic factors influencing the sex hormones which modulate the immune response, including the specific role of genes in the major histocompatibility complex.
- A project examining the role of influenza virus in autoimmunity as a possible etiologic factor in rheumatic disease, under way at the University of Alabama in Birmingham.
- A project to develop new imaging techniques to detect pathologic changes in cartilage and bone in patients with osteoarthritis, being conducted at the University of Michigan's center in Ann Arbor.

- Studies of joint replacement surgery at the Brigham and Women's Hospital Center in Boston, with the goal of developing methods to evaluate the suitability of patients for surgical procedures by means of gait analysis.

- Development of a procedure at Case Western Reserve University's Center in Cleveland, to reproduce lumbar spinal stenosis in an animal model in order to study neurological changes induced by this disorder.

- Investigations at Northwestern University in Chicago, of two potential infectious etiologies for Kawasaki syndrome: the first, a viral etiology, using peripheral blood cells as a model; and the second, caused by toxins produced by bacteria.

- Examination of the effector mechanism for development of congenital complete heart block, often found in patients with neonatal lupus, at the center at the University of Missouri in Columbia.

- An investigation to test whether biopsy of the femoral head is a useful and safe procedure to make a diagnosis of avascular necrosis in patients with systemic lupus erythematosus, being carried out at the University of Connecticut center.

- Development of an animal model of chronic, erosive arthritis in rats, under way at the University of North Carolina at Chapel Hill, to examine the role of lipopolysaccharides (substances derived from the bacterial cell wall) in the immune process.

## Center Education Projects

Educational activities designed to facilitate the education of diverse types of health professionals, devoted to caring for patients with rheumatic diseases, are another important aspect of Multipurpose Arthritis Centers. Examples of projects in this area are:

- A project to create a computer-based rheumatology instructional unit for medical students and residents for the purpose of enhancing learning of rheumatological diagnostic and management skills, developed at the University of Missouri in Columbia.

- Initiation of a program, at the University of Connecticut in Farmington, to develop methods of arthritis patient education targeted to black and Hispanic adults with low literacy.

- A study designed to reduce the incidence of lifting-related back injuries and musculoskeletal injuries to the neck, shoulders, chest, thighs and hips in Boston postal workers, carried out by the Brigham and Women's Center.

- Development of an education program, under way at the University of California Center in San Francisco, for use in home health agencies, to train nurses and nursing aides to improve patient care, patient education, and thus improve patient outcomes.

- An assessment, conducted at the Boston University Center, of rheumatologic skills displayed by third-year postgraduate physicians with the goal of developing and offering a remedial education plan for residents with little or no experience in rheumatology.

## Center Community Health Services Research Projects

Community health services research projects at the Multipurpose Arthritis Centers span activities ranging from health-related economics to epidemiology to the effect of chronic illness on the quality of life.

Specific examples are:

- An epidemiologic study of osteoarthritis, under way at the University of Michigan Center in Ann Arbor, in a population sample of the Tecumseh Community Health Study to identify factors that contribute to pathogenesis of disease.

- Continued expansion and assessment of the Arthritis Impact Measurement Scale (AIMS) instrument developed at the Boston University Center. This questionnaire is designed to measure health status of patients with arthritis in terms of several aspects including mobility, dexterity, social activity, depression, activities of daily living and pain.

- A study, also at Boston University, seeking to discern a relationship between social and psychological stresses and the course of rheumatoid arthritis.

- A controlled prospective study at Stanford University to analyze effects of long-distance running on the rate of development of radiologic signs of osteoarthritis and musculoskeletal disability.

- An exploration of relationships between type A behavioral patterns and other aspects of the emotional and behavioral responses and rheumatoid arthritis, being conducted at the Indiana University Center in Indianapolis.

- An investigation of immunogenetics of familial rheumatoid arthritis, by investigators at Case Western Reserve University's center in Cleveland, to develop a method of calculating the risk of developing rheumatoid arthritis.

- A study at Northwestern University in Chicago to investigate the prevalence of musculoskeletal disease in the elderly, and test cost-effective intervention strategies aimed at maintaining independent functioning.

- An investigation, at the University of Texas in San Antonio, to determine the efficacy of transcutaneous nerve stimulation and trunk exercises for patients with low back pain.

- Application of the mathematical techniques of set theory, being tested at the University of Connecticut center, to characterize various subsets of patients with systemic lupus erythematosus.

## Core Units

These common-use facilities are designed to increase the effectiveness and efficiency of each center's research activities. There are biomedical research core units for tissue culture, connective tissue metabolism, immunology, histocompatibility testing, and research involving hybridomas. Other research core units are concerned with biostatistics, evaluation methodologies, educational projects, and epidemiologic research.

A research core unit on protein structure at Indiana University, for

example, has been utilized to provide amino acid analyses, protein sequencing, immunoelectrophoresis, and peptide analyses.

Another core unit, dealing with immunology research, functions as a centralized facility carrying out specialized tests of human immune function, including assays for immune complexes, *in vitro* antibody synthesis, and assessment of T and B lymphocytes in peripheral blood.

A hybridoma core unit at the University of Alabama Center in Birmingham is being used to produce monoclonal antibodies for investigators at the center.

A core unit at the University of Michigan's center provides investigators with tissue culture support for projects dealing with the biologic function of scleroderma skin fibroblasts, responsiveness of human osteoarthritic chondrocytes grown in culture, and possible defects in proteoglycan protein synthesis.

A core for amyloid research at the Boston University center facilitates research in cell biology, molecular biology, biochemistry, and immunohistochemistry and immunoelectron microscopy.

Core units dealing with research planning and statistics are in operation at the arthritis centers at the University of Connecticut, the University of North Carolina, Boston University, Stanford University, and Northwestern University, providing expertise in research design, data collection, data base management, computer programming, and data analysis.

## Collaboration Among Centers

This is accomplished through annual meetings of the center directors, other key center personnel, and Institute staff administering the program. The NIAMS centers program office also compiles and updates annually a directory of center personnel, and is in regular contact with each center by means of letters and phone calls. The centers have been encouraged to utilize the services of the Arthritis Information Clearinghouse, funded by contract

by the NIAMS, as a repository for educational and other informational materials.

## Center Evaluation

Several types of evaluative activities are employed to assure that the goals addressed by each center are being fully and successfully implemented. These include measures of the value and effectiveness of each project, conducted by the centers themselves, often involving special evaluation core units; and the use of outside consultants to visit a center for several days at a time each year to determine the quality of ongoing activities. In addition, the centers program office of the NIAMS carefully monitors the work of the various centers through means of staff site visits, analysis of yearly progress reports, letters and telephone calls, and the indepth annual meeting of the center directors.

## Conclusion

The Department of Health and Human Services finds that the Multipurpose Arthritis Centers are continuing to progress significantly toward achieving their congressionally mandated objectives. During the past year this progress has been particularly evident in both biomedical and health services research. The program continues to mature, in terms of high-quality research developments and prompt application of research findings.

# The Biennial Report of the Director, Division of Research Resources

## History

The following events represent milestones in the development of the Division of Research Resources (DRR).

- July 30, 1956—The Health Research Facilities Act of 1956 (Title VII of the PHS act) authorized a PHS program of Federal matching grants for the construction, expansion, remodeling, or alteration of non-Federal, nonprofit facilities engaged in research in "the sciences related to health."

- August 19, 1959—Congress appropriated \$2 million for the establishment of one or two regional primate research centers. Additional funds were appropriated in FY 1961 and 1962, resulting in the establishment of seven centers altogether, six of them designated as regional and one as national.

- September 15, 1960—P.L. 86-798 amended the Public Health Service Act to authorize grants-in-aid to universities, hospitals, laboratories, and other public and nonprofit institutions to strengthen their programs of research and research training in sciences related to health. The act also authorized the use of funds appropriated for research or research training to be set aside by the Surgeon General in a special account for general research support grants.

- April 13, 1962—The Surgeon General, PHS, announced the establishment of the new Division of Research Facilities and Resources (DRFR) to administer NIH's construction-related activities, general research support grants, the primate centers, and the general clinical research centers.

- September 24, 1963—P.L. 88-129 amended the Public Health Research Facilities Act of 1956 to allow grants for multipurpose facilities that would provide teaching space as well as essential research space.

- October 31, 1963—P.L. 88-164, the Mental Retardation Facilities and Community Mental Health Centers Construction Act of 1963, authorized a total of \$329 million over a 5-year period for matching grants to assist in the construction of mental retardation research centers and community mental health centers, and to train teachers of mentally retarded and other handicapped children.

- August 9, 1965—P.L. 89-115 extended Title VII, Part A, for an additional 3-year period and authorized an aggregate appropriation of \$280 million for FY 1967, 1968, and 1969.

- August 16, 1968—P.L. 90-490, the Health Manpower Act of 1968, extended Title VII, Part A, for an additional 2-year period and authorized \$20 million for FY 1970 and \$30 million for 1971.

- January 4, 1969—A notice in the Federal Register renamed DRFR as the Division of Research Resources, placing it within the Bureau of Health Professions Education and Manpower Training (BHME), then part of NIH, and moving the Health Research Facilities Branch to the Division of Education and Research Facilities, also within the Bureau.

- September 18, 1970—The Division of Research Resources was separated from BHME and became a separate Division within NIH. At that time, the Division included the then recently formed special research resources program, now known as the Biomedical Research Technology Resources Program, and the Laboratory Animal Sciences Program that had been created in 1963.

- 1970 to 1985—Since its establishment as one of NIH's independent research Divisions, DRR has added the Minority Biomedical Research Support Program in 1972; the Minority High School Student Research Apprentice Program in 1980; the Shared Instrumentation Grant activity in 1982; and the Biological Models and Materials Resources Section and the new Animal Facilities Improvement Program in 1985.



• 1982—Dr. Betty H. Pickett was named Director of the Division.

• November 20, 1985—P.L. 99-158, the Health Research Extension Act of 1985, established the Division and its advisory council in law.

## Introduction

The Division of Research Resources supports resources essential to the conduct of biomedical research. The major programs of DRR are: Biomedical Research Technology Resources, which provides access to the latest technologies from the physical sciences, mathematics, and engineering; General Clinical Research Centers, which are specialized clinical research units, usually within larger hospitals; and Animal Resources, which support the effective use of laboratory animals, in addition to supporting the seven Regional Primate Research Centers and other unique animal colonies. The Division also awards Minority Biomedical Research Support Grants to increase the participation of ethnic minorities in the biomedical sciences; Biomedical Research Support Grants to enhance the effectiveness and efficiency of biomedical research and behavioral research related to health at institutions receiving Public Health Service (PHS) grant support; and Shared Instrumentation Grants to make available to institutions major research instrumentation on a shared-use basis for groups of PHS-funded investigators.

The Division undergirds the research activities of more than 5,400 PHS-supported biomedical investigators by developing and providing the resources needed by the research community to accomplish their research.

Research accomplishments facilitated by DRR-supported resources span the breadth of the NIH mission. In FY 1985, many DRR resources provided support for research in the areas of genetics and biotechnology. For example, the Animal Resources Program (ARP) described the use of genetic engineering techniques to produce

growth hormone; the General Clinical Research Centers (GCRC) Program reported on the potential for gene transfer therapy of selected inherited diseases; and a significant proportion of the instruments purchased through the Shared Instrumentation Grant (SIG) Program contributed to basic and applied research in these areas. A major use of resource funds was for research in endocrine and metabolic pathophysiology. The GCRC Program, for example, supported research leading to increased understanding of essential hypertension by determining the effect of a polypeptide hormone on salt metabolism and blood volume. Research in immunology is an important component of DRR resource grants. Under the SIG Program funds for protein sequencers were awarded to study tumor antigens or tumor markers. The Minority Biomedical Research Support (MBRS) Program continues to support work on steroid therapy for breast cancer and on schistosomiasis, and the Research Centers in Minority Institutions (RCMI) Program is contributing to the development at one institution of an immunogenetics laboratory. Equally important is support for research in neurobiology; for instance, the Biomedical Research Technology Program (BRT) described mass spectrometric studies on a model for Parkinson's Disease. ARP-assisted AIDS research has identified a monkey model which may be used in the development and testing of candidate vaccines for AIDS, and the GCRC Program continues to support research on new treatment protocols for this disease.

DRR plays a critical role in support of the research infrastructure. As an example, BRT both develops and provides state-of-the-art instrumentation to investigators on a regional or national basis, while the SIG Program awards funds for instruments such as electron microscopes, cell sorters, fermentors, and image analysis equipment for shared use on a local scale. A major focus of the RCMI Program is to improve the facilities for research

at doctoral degree-granting minority institutions, and the MBRS Program provides funds for equipment, alteration and renovation, and enrichment activities, as well as support for faculty research projects at a broad range of institutions serving minorities. In addition, the ARP continues to address the substantial need for improved animal facilities through an expanded initiative, announced in FY 1985, to support alteration and renovation of animal facilities. Funding also has been provided to upgrade the facilities of the Primate Research Centers. An important facet of the Division's support is its education of medical research manpower through its NRSA training programs for laboratory animal scientists, through the research opportunities provided to minority students by the MBRS and Minority High School Research Apprentice Programs, and by the Clinical Associate Physician Program of supplemental awards to GCRCs.

Currently, the staff and advisors to the Division are considering several major policy issues, such as:

- Can guidelines be put in place to accelerate the GCRC Program's response to national health needs such as rapid development of a vaccine against and therapies for AIDS, urgent new cancer therapy trials, or cooperative clinical studies?

- Should the SIG Program consider including funds for maintenance and/or repair of the instruments it awards or should the Program continue providing modern instruments to the largest possible number of investigators?

- Can DRR estimate the impact of terminating the Biomedical Research Support Grant (BRSG) formula award on scientific productivity and health manpower training?

- While the MBRS Program has seen substantial success in providing research experiences for students at minority institutions, could it better achieve its long-range goals if it were provided with NRSA training authority?

• Many NIH grantee institutions are in need of funds to build new research animal facilities. Three Institutes have construction authority, but these programs do not directly focus on animal facility needs. The Division's current animal facilities improvement program is making a modest beginning in addressing alteration and renovation needs. However, the Division does not have the necessary legislative authority to allow applicant organizations to request NIH funds to construct new animal facilities when necessary. Can the Division determine how many institutions that request funds for alterations and renovations of their animal facilities actually would find new construction the most cost-effective method of upgrading these facilities?

• PL-99-158 requires the Director, NIH, to develop and implement a plan to examine research methods which do not require the use of animals, to reduce the number of animals used in research, or reduce the pain and distress of animals used in research. The Division, and particularly the new Biological Models and Materials Resources (BMMR) Section, has lead responsibility for developing this plan for NIH. The Division is examining how the BMMR section will implement this plan.

• Each of the Division's resource programs is considering carefully the duration of support for individual resource awards, when continuation applications are renewed. Are more formal program policies needed?

In the following sections, the purpose, recent progress, future priorities, and policy issues of each of the Division's major programs, plus the Research Centers in Minority Institutions Program are detailed.

### **General Clinical Research Centers Program**

#### *Purpose*

The goal of the General Clinical Research Centers (GCRC) Program is to provide clinical research resources for those investigators

supported by the categorical institutes of the NIH or by other peer reviewed sources of funding. The resources include patient care facilities with appropriate nursing and dietary support, sophisticated laboratory technologies including computer hardware and software for study design and data analysis. These facilities provide the opportunity for interaction of basic and clinical research. The GCRC Program provides a unique setting for future clinical investigators by providing examples of scientific protocols, investigator role models, and specialized training.

### **Research Highlights**

#### *Acquired Immune Deficiency Syndrome*

AIDS studies, under way at several of the GCRCs, are designed to characterize the natural history, factors altering host susceptibility, and mechanisms by which HTLV-III induces altered immune function. Since AIDS patients usually die within 2 years of diagnosis, the current focus is on a variety of therapeutic agents including recombinant interleukin-2, recombinant gamma interferon, and agents which interfere with replication of HTLV-III within the infected cells. The rationale for using gamma interferon and interleukin-2 is based on empirical observations that affected patients' T-cells, a subclass of circulating white cells, fail to make interleukin-2, an important immunoregulatory substance. Additionally, the T-cells of patients with AIDS fail to make gamma interferon, a substance which activates another class of white cells, termed macrophages, which are important for helping the patient react to infection. The GCRC support for these studies includes hospitalization costs, nursing, and ancillary services.

#### *Atrial Natriuretic Factor and Hypertension*

The interaction among several humoral and dietary factors associated with hypertension is studied at many centers. Atrial

natriuretic factor (ANF) is a polypeptide hormone isolated and purified from the upper two chambers of the heart. The effect of ANF on salt metabolism and volume of fluid in the circulatory system has been studied in several abnormal states including essential (unknown cause) hypertension, congestive heart failure, and kidney dysfunction. Increased total circulating blood volume, as seen in heart failure patients, is an important stimulus for ANF secretion. Research on this hormone may improve therapeutic strategies for the treatment of hypertension, congestive heart failure, and other diseases of the circulatory system. Core laboratories supported at many of the GCRCs are providing many of the specialized biochemical analyses required in these studies.

#### *Molecular Cloning and Clinical Research*

The transfer of molecular cloning techniques to the clinical arena has become a reality. These important techniques are used for identifying carriers of genetic disorders and provide the data used in genetic counseling. The sensitivity of these techniques has provided insight into the molecular basis for several disease states. For example, some forms of insulin resistance are secondary to an alteration of a portion of the insulin receptor. There is now potential for gene transfer therapy of selected inherited disease states; many of these diseases are currently not treatable. For example, Lesch-Nyhan syndrome is a markedly abnormal clinical state characterized by mental retardation, abnormal muscle control, and uncontrollable self-mutilation. It results from the absence of a single enzyme. Introduction of the gene which controls the synthesis of the missing enzyme into affected hosts may alleviate the severe symptoms of this disorder. The gene which controls the synthesis of the enzyme in human cells has been successfully inserted *in vitro* into cells normally found in the bone marrow and could potentially lead to a method to introduce gene expression of the enzyme into affected individuals. GCRC-funded beds and



*Molecular cloning techniques are now being used to identify carriers of genetic disorders. The sensitivity of these techniques has provided insight into the molecular basis for several disease states.*

the associated care laboratories are resources critical for these studies.

#### *The Diabetes Control and Complications Trial*

Several of the centers are participating in the DCCT by providing inpatient and outpatient facilities as well as a cadre of research nurses. The multicenter study represents a randomized, prospective trial designed to assess different insulin regimens to ascertain whether more intensive insulin therapy may prevent or delay the serious complications of diabetes mellitus. When blood sugar levels are lower than normal, several hormones and epinephrine increase glucose production from the liver. Many diabetics have abnormal function of their autonomic nervous system, resulting in decreased levels of epinephrine, an agent important for counteracting the effects of low blood sugar. Since carefully controlled diabetics are more likely to have low blood sugars, those individuals with diabetic autonomic neuropathy are at increased risk for severe hypoglycemia (low blood sugar) and permanent brain damage. Based on those observations, investigators in the DCCT suggest that diabetics with impaired autonomic function not be subjected to rigorous insulin therapy for maintaining normal blood sugar

levels until some remedy (such as an accurate, implantable, blood sugar sensor with appropriate audible signals) can be perfected.

#### *Pancreatic Transplantation*

A variety of approaches have been undertaken to treat diabetics, including pancreatic transplantation. The 1-year pancreatic graft survival rate is approximately 40 percent, and in some patients with functioning pancreatic grafts there has been reversal of diabetic kidney disease. However, in others progressive diabetes-associated abnormalities affecting the eyes; the nervous system, and kidneys have occurred, prompting research to determine whether earlier selection and more aggressive control of even mild-degree glucose intolerance will provide better protection from the development of diabetic complications. GCRCs are being utilized for pre-surgical observation as well as for evaluation of the patients following transplantation.

#### **Future Opportunities and Priorities**

A closer integration of the clinical research needs of the categorical institutes and the GCRCs will be facilitated. Future Plans include computer networking of all centers to facilitate uniform data reporting on multicenter research projects and trials. Moreover, with changing patterns of health care delivery, increased emphasis will be given to outpatient studies as well as to providing specialized study facilities. Moreover, specialized resources within GCRCs will enhance and expand center utilization, examples would be: centers which include specialized equipment for cardiovascular studies, imaging techniques for studying selected brain centers and their interactions with systemic disease, forms of epilepsy, and Alzheimer's disease. Training of physician investigators has been an important adjunct of the GCRC Program since its inception. Formalized in 1974 as the Clinical Associate Physician (CAP) award, the Program has supported opportunities for 173 post-resident physicians to gain experience, over a 2- to 3-year

period, as clinical research investigators. Of the 135 who have "graduated" from the program, 101 are currently in academic medicine. Training of physician-investigators will continue to be a high priority and opportunities for more sophisticated training in newer technologies will be emphasized.

#### **Policy Issues**

The high costs of medical care are reflected in the operational costs of the 78 GCRCs throughout this country. The trend of health care delivery has been toward shorter hospital stays and more outpatient testing. The effect of Diagnosis Related Groups (DRGs) and Health Maintenance Organizations (HMOs) on GCRC utilization and cost is of prime concern, but such effects cannot be adequately assessed until more information is available.

In FY 1986, a few centers attempted a small, retrospective study on patients whose hospitalization was covered by Medicare or other third party payers. The study showed mixed results, but highlighted the need to develop uniform strategies to enable the centers to collect good prospective data. When these strategies for accumulating prospective data are implemented, the data may shed some light on whether certain types of research protocols require hospitalization in excess of current DRG allocations.

### **Biomedical Research Technology Program**

#### **Purpose**

The goals of the Biomedical Research Technology Program are to identify and develop advanced technologies needed in biomedical research and provide investigators access to these technologies for use in research investigations. The Program accomplishes these goals primarily through funding resource grants. Other support mechanisms used, designed to complement the resource grant, are resource-related research project grants, small grants, first independent research support and transition awards, cooperative agreements, contracts, and Small Business Innovative

Research grants. Areas of emphasis in the Program are biomedical computing, biomedical engineering, and technologies for the study of biomolecular and cellular structure and function.

### Research Highlights

*Primary Eye Care: A Treatment Guide Using a Portable Computer*  
In developing countries, blindness is a major health problem where control depends on the application of simple measures by frontline health care providers. Unfortunately, in many of these countries, medical care by physicians is not readily available. To assist primary health workers in the management of common and potentially blinding eye disorders, research scientists at Rutgers University, the University of California in San Francisco, and IBM have collaborated to develop a computer program based on artificial intelligence methods for a hand-held computer that incorporates a set of guidelines for diagnosis and treatment based on the World Health Organization guide to primary eye care. The approach became feasible because of recent advances in expert system and portable computer technology.

The research resource at Rutgers University had developed a generalized medical consultation model, the expert system that provided the basis for this project. The model components are findings, hypotheses, and decision rules. Findings are observations such as the patient's history, symptoms, and lab results. Hypotheses are conclusions inferred by the system, and include diagnostic possibilities and therapy recommendations when appropriate, and intermediate hypotheses about the condition with requests for further information in other situations. The decision rules are a series of "if-then" rules which are the basis for the system. These are developed and modified on the basis of test cases to lead to optimum performance.

The model is based on the World Health Organization's primary eye care guidelines. Findings are based on a series of questions and rules

that lead to a presumptive diagnosis, followed by another set of rules recommending treatment.

Problem management by the health worker involves one of three actions:

- Treatment with no referral necessary.
- Initial treatment with referral to a secondary center.
- Referral with no treatment.

Direct treatment tends to be limited to topical antibiotic application for bacterial conjunctivitis, and warm compresses for sties. Treatment and referrals would apply to problems such as corneal ulcers; more serious cases are directly referred to district hospitals. The health worker is guided towards a diagnosis and recommended treatment through computer questions and answers. Thus, the program is also intended to raise the competence of the workers in standards of eye care delivery.

Evaluation is continuing in two California eye clinics, and field evaluation is planned for Tunisia and Egypt. The Agency for International Development also supports the activity.

### *Loop, Gap Resonators Enhance Magnetic Resonance Imaging and Spectroscopy*

Loop gap resonators, developed at the National Biomedical Electron Spin Resonance (ESR) Center in Milwaukee, Wisconsin, are a new class of microwave resonators that yield a remarkable increase in ESR sensitivity. This major advance in ESR instrumentation is being applied to magnetic resonance imaging and <sup>31</sup>P magnetic resonance spectroscopy.

Using this new method, the first *in vivo* <sup>31</sup>P magnetic resonance spectroscopy of the adult human liver and the first imaging of the rotator cuff of the shoulder (a key site for many sports-related injuries, especially of baseball players) have been performed. At the Medical College of Wisconsin, many other anatomic structures have also been imaged with exceptional resolution. This technique has provided the highest resolution of anatomic structures yet available for local regions of the body and should

lead to correspondingly accurate biochemical information *in vivo*.

This new combination of magnetic resonance imaging and spectroscopy will enable resolution superior to any other current method. Based on this work, collaboration has begun with two other DRR resource centers at Stanford and at the University of Wisconsin. It is anticipated that these collaborations will expand the applications of this new technique.

### *Mass Spectrometric Studies of a Drug that Produces Parkinson's Disease*

The compound 1-methyl-4-phenyl-tetrahydropyridine (MPTP) is a neurotoxic by-product of illicit drug manufacture. It produces permanent Parkinson's disease in humans which is clinically identical to idiopathic Parkinson's disease. The substance appeared in Santa Clara, California in 1982, and it produced widespread interest as a model for Parkinson's disease. Investigators at the University of California in San Francisco Mass Spectrometry Resource are presently studying the metabolism of this compound in various animal tissues and the mechanism of its potent neurotoxicity. Mass spectrometry is required for the identification of the metabolites of this compound. It appears that the metabolism of MPTP to a more toxic substance is the cause of the neurotoxicity. Studies of MPTP neurotoxicity will provide clues to the origin of Parkinson's disease in man, since this is the first time Parkinson's disease has been chemically induced.

### *Molecular Mechanics Computing System*

A new type of computing system for molecular mechanics calculation has been designed and is being built at the Columbia University Research Resource in collaboration with engineers at the Brookhaven National Laboratory. The system will provide greatly increased computer power to investigators concerned with properties and functions of protein molecules as well as the interactions of proteins with

smaller molecules such as drugs. The system is composed of a very fast general purpose array processor and an optimized, special purpose processor called FASTRUN.

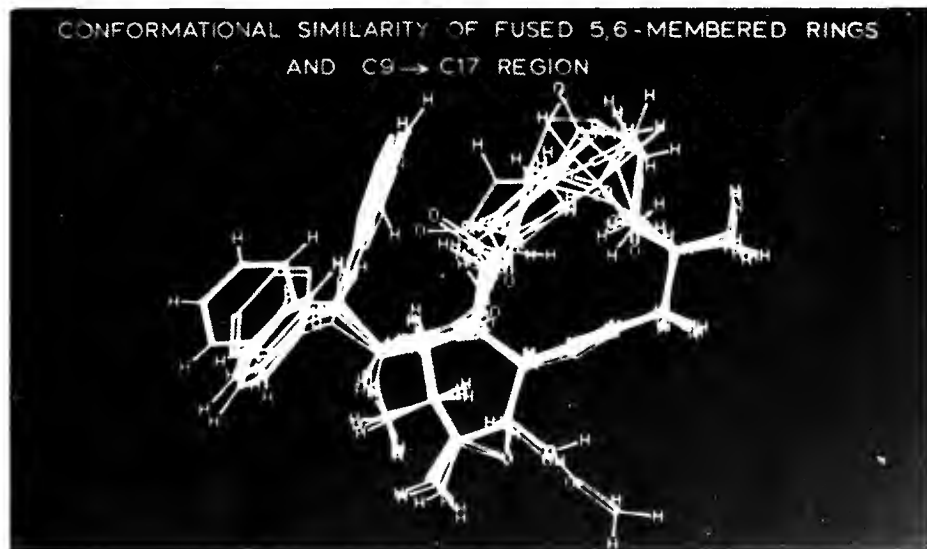
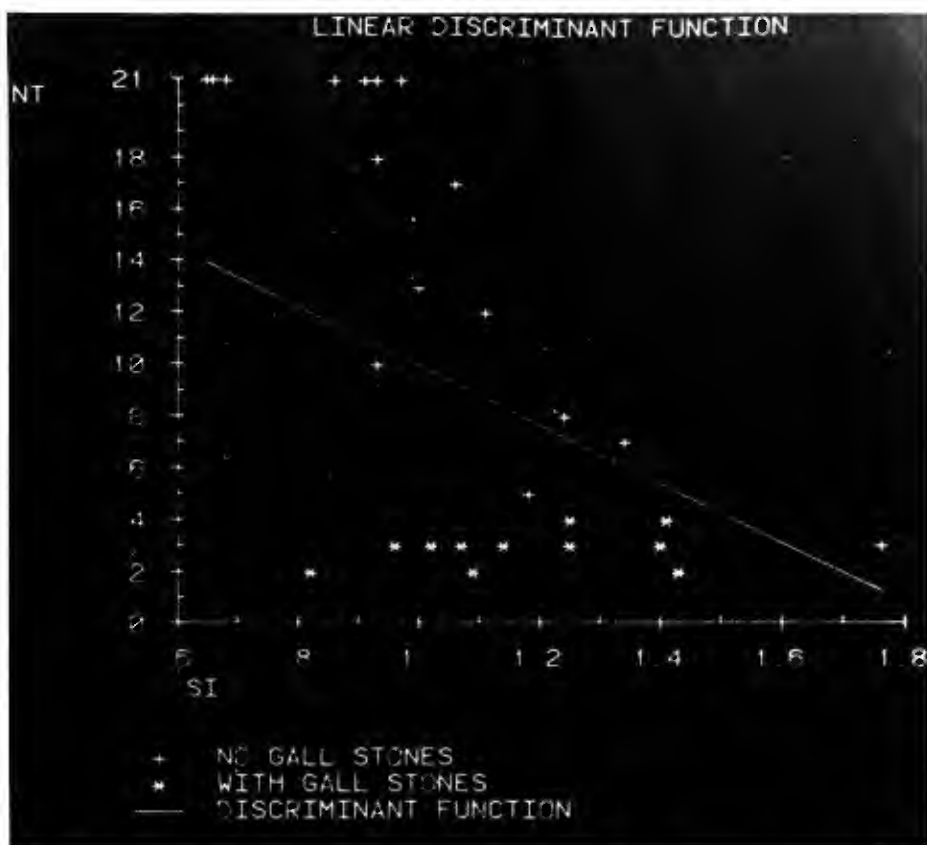
FASTRUN will calculate the forces and energies due to the interactions of atom pairs, which may be as many as 2 million for a large protein. The array processor, which is about 10 times slower than FASTRUN, calculates the forces and energies due to the bending and twisting of chemical bonds. There are about 100 times as many pairwise interactions affecting the atoms of a protein as there are bond bends or twists. Since both devices do their calculation simultaneously, the use of FASTRUN with the array processor will have about the same power for molecular calculations as the most powerful supercomputer expected within the next few years. In contrast, however, the cost to replicate this system will be about one-twentieth of the cost of a large supercomputer. This system is scheduled to be completed in the fall of 1986.

### Future Opportunities and Priorities

#### *Access to Supercomputers for Biomedical Scientists*

The term "supercomputer" is used to designate the most powerful computer currently available. Today's supercomputers have capabilities measured in terms of hundreds of millions of "floating-point" operations per second. It is becoming obvious that supercomputers have numerous applications in the biomedical sciences and, in fact, that many problems heretofore unsolvable can now be addressed through the use of supercomputing capabilities.

Such problems include: the analysis and modeling of dynamic processes ranging from the determination of molecular conformation to the dynamics of organ and body functions, the analysis of large data bases such as those obtained from DNA sequence analysis, and the manipulation and enhancement of images of biomedical interest.



The PROPHET computer system, a nationally available resource, is used in virtually all areas of biomedicine to store, manipulate, and graphically display experimental data. A revised version, PROPHET II, is now being developed as a successor to the present system.

A joint program between NSF and NIH, announced in February 1986, will provide NIH investigators up to 25 hours on NSF-supported supercomputers. These researchers will explore the potential advantages of the supercomputer in their biomedical research projects.

In FY 1987 the program plans to award a cooperative agreement for 3 years to an established supercomputer center to provide supercomputer access for research and training for biomedical scientists.

*The PROPHET Network: A Computer Network for Biomedical Research and Communication*  
The PROPHET Computer Network provides biomedical researchers with a comprehensive, integrated set of interactive graphic and data analysis tools. PROPHET's capabilities include data storage, management, and visualization; statistical analysis, curve fitting, mathematical modeling and simulation; and molecular modeling and amino acid and nucleotide sequence handling. Through PROPHET's national telecommunications system, data may be entered, accessed or analyzed from any location within the country. Scientific collaborations and shared research projects can be supported among investigators located at widely separated sites.

The PROPHET Computer Network links about 1,000 biomedical scientists at nearly 50 locations working in many specialties including cardiovascular studies; investigations of drug design; and efficacy, immunology, hematology, and studies of the nervous, sensory, and urinary systems.

The BRTP is supporting a contract for the development of a second generation of PROPHET capabilities. Using modern distributed computer technology, intelligent graphic work stations will perform all but the most complex PROPHET tasks. Scientists may connect to local PROPHET host machines or a centralized facility for the largest of their tasks or for access to large, shared data bases. The new system is scheduled to be operational in November 1987 when many more scientists will be able to use PROPHET.

## Policy Issues

The Biomedical Research Technology Program conducted an analysis of its 3-year-old small grant program. As a result, the small grant ceiling was raised from \$15,000 to \$25,000 with the expectation that the additional money would allow applicants to focus on more advanced technologies. The Program will monitor the nature of the small grant applications to determine if this expectation is realized.

Another BRTP evaluation, of the need for additional training in the Program's resource technologies, resulted in two actions to strengthen this area. First, supplemental grants were awarded to 11 institutions to increase their training efforts. Second, the Program gave a stronger emphasis to training by encouraging all institutions to stress this activity. The Program will continue to review the adequacy of training provided at BRTP centers.

The amount and duration of support for individual resources have been periodically examined. The annual budget limit of \$650,000 direct costs, excluding equipment, is realistic, and only a small number of resource applications have requested a waiver from this ceiling. In the past, considerable discussion has been directed toward placing a limit on the duration of support for a resource. The premise was that after a specified amount of time, approximately 10 years, resource technologies are no longer considered advanced. However, most grantees continue to develop or purchase new equipment as well as develop new technological methods and techniques as part of their core research and development activities. Because of these activities, a 10-year limit is deemed too restrictive. Instead, a policy requiring resources to propose new technological research and development activities in competing renewal applications was implemented. To be renewed, resources must be judged meritorious in their technological research proposals as well as in the

other resource activities of collaboration, service, training, and dissemination of information. This policy will ensure that resources continue to offer the most advanced technologies to researchers.

## Animal Resources Program

### Purpose

The Animal Resources Program of the Division of Research Resources supports resource activities that make more effective use of laboratory animals and other biological models in research projects funded by NIH categorical Institutes and that have a direct impact on animal health and welfare. This is accomplished through resource support for biomedical research conducted in the seven Regional Primate Research Centers, the provision of diagnostic and laboratory services, development of research manpower in laboratory animal sciences, the development of animal and special nonanimal biomedical models, the improvement of laboratory animal facilities, and provision of other research services which support NIH categorical programs.

The Animal Resources Program also assists the Office of the Director, NIH, in the development of guidelines for the humane care and use of animals in research, and serves as liaison to various animal welfare and professional scientific societies interested in the care of laboratory animals. The three components of this Program are the Regional Primate Research Centers Program, the Laboratory Animal Sciences Program, and the Biological Models and Materials Resources Section.

### Research Highlights

#### *Growth Hormone from Genetic Engineering*

Using the latest molecular biological techniques, a nonpathogenic vaccine strain of herpesvirus was genetically manipulated by scientists at the New England Regional Primate Research Center to construct a virus that contained the gene for producing growth hormone. Cells infected with this strain



of virus produced large amounts of growth hormone for long periods of time—a finding that may have practical importance for industrial and human medical applications. Monkeys inoculated with this strain of virus showed increased levels of circulating growth hormone but did not experience more rapid growth. This work offers a good potential approach to gene therapy for correcting inborn errors of metabolism through genetic engineering.

#### *AIDS Vaccine*

Research and surveillance studies of naturally occurring and experimentally induced retroviral infections in nonhuman primates are becoming more important as relationships both to the human AIDS research effort and to the health of nonhuman primates used in research are increasingly recognized. These studies have resulted in the identification and initial characterization of monkey models that may play a pivotal role in the development and testing of candidate vaccines for AIDS, as well as evaluation of approaches to the treatment and prevention of this disease. An HTLV-III-like lentivirus (initially isolated at the New England Regional Primate Research Center) inoculated into rhesus monkeys is probably the most promising model. It is similar structurally to the AIDS virus and causes a disease in monkeys that is like that seen in humans in many of its clinical and pathological features. Evidence of latent retroviral infection in many other monkeys suggests that the occurrence of possibly immunosuppressive and transmissible retroviruses is widespread and represents a potentially serious health problem in research primate colonies.

#### *Diagnostic and Investigative Laboratories*

The objectives of resource laboratories are: (1) to provide for improved laboratory animal health programs through appropriate surveillance activities and investigation of naturally occurring disease and other laboratory animal problems and their etiology, (2) to aid in

the elucidation of new animal models of human disease, and (3) to develop resources for research and training. For example, although diarrhea is the second most important laboratory rabbit disease that complicates research, the cause has been difficult to determine and represents a common problem for animal diagnostic laboratories. Because viruses of the rotavirus group are an important cause of diarrhea in other animals and humans, one resource laboratory has investigated whether there is any association of rotaviruses with disease in rabbits, and whether the infection in rabbits represents a potentially productive animal model for the infection in humans. Pilot projects have revealed that about 25 percent of the stools from diarrheic rabbits and 10 percent of those from healthy rabbits contain rotavirus, that the agent can cause severe, life-threatening enteritis in seronegative animals. Two strains of virus have been isolated in tissue culture and an ELISA test, developed for the detection of antibodies, showed that approximately 90 percent of the adult rabbits tested had antibodies to rotavirus. Continuing, in-depth studies on the subject are expected to contribute valuable information on both the cause of disease in laboratory rabbits and the biology of rotaviruses in other species, especially humans.

#### *Cryopreservation of Murine Germplasm*

The long-term objective of the project, Cryopreservation of Murine Germplasm, is to establish a bank of frozen mouse embryos to preserve mutants and strains of mice that are valuable to many fields of research. In many cases, cryopreservation will allow a reduction in the number and size of colonies maintained by conventional breeding procedures and will also serve to retard genetic drift. Freezing techniques, using eight-cell embryos, frozen at a controlled rate and stored in liquid nitrogen, are now well established. More than 425,000 embryos have been frozen

and stored from approximately 450 different strains since the project's inception 4 years ago. To date, over 40 strains have been terminated from active breeding because they have been safely preserved. Seven strains were reconstituted successfully last year for research use, including one strain that was recovered to replace breeding stock that was lost.

### **Future Opportunities and Priorities**

#### *Manpower Development*

Well trained investigators with a background in laboratory animal science and medicine are essential to biomedical research. The number of specialists in the field certified by the American College of Laboratory Animal Medicine has increased only 9 percent (263 to 294) in the last 5 years. Such individuals are needed to establish new diagnostic resources, lead the search for additional animal models, and help solve problems of disease in laboratory animal colonies. They are also needed to help establish and staff centralized programs of laboratory animal care in many NIH grantee institutions. The new PHS Animal Welfare Policy requires that Institutional Animal Care and Use Committees have one member with a D.V.M. degree. This individual must have training or experience in laboratory animal science and medicine and have direct or delegated program responsibility for activities involving animals at the institution. The Division supports both institutional training programs and postdoctoral fellowships to meet this need. However, the current number of graduates from ARP-supported training activities (12 to 15 a year) is clearly inadequate. A number of diplomates have reached or will shortly reach retirement age. The current rate of training does not meet the growing need.

#### *Biological Models and Materials Resources Section*

In February 1985, the new Biological Models and Materials Resources Section was established within the Animal Resources Program, Division of Research Resources. The

section's mission is to develop and support cell systems, lower organisms and nonbiological systems as models for biomedical research, and to provide biological materials serving as critically important resources to the research community. Currently the section is addressing the need to explore and support the utilization of nonmammalian models in biomedical research.

The report from a 1984 study by the National Academy of Sciences serves as the major guide for the development of the new section's programs. The report evaluates the opportunities and limitations to the use of simple model systems in biomedical research. Its recommendations are that NIH should: (1) strive to make favorable systems readily available to the research community by providing support to supply organisms for research, maintaining stock centers for mutant strains and cell lines, facilitating access to computer programs for biomedical modeling, maintaining data bases like those for protein and DNA sequences, and providing long-term support for collections of cloned genes and useful vectors or collections of monoclonal antibodies; (2) consider supporting development of new model systems for specific research areas; (3) consider encouraging interest in nonmammalian systems through fellowships, symposia, and direct support of model development; and (4) investigate the concept of the matrix of biological knowledge as a potential tool for biomedical research.

**Chimpanzee Research and Breeding**  
Chimpanzees are the only surrogate for man in some research and testing, and it is in the national interest that these animals continue to be available for these purposes. They are principally used in studies of viral hepatitis and certain other viral diseases including AIDS, where no other animal or nonanimal model system is better. The number of chimpanzees is dwindling, and none have been imported from the wild for research since 1974 when the United States



*The chimpanzee: the only surrogate for man in some research and testing. Chimps are used principally in studies of viral hepatitis and certain other viral diseases where no other animal or nonanimal model system is better.*

became a signatory to the Convention on International Trade in Endangered Species. Current captive management practices will result in zero production of chimpanzees in the United States within the next 25 years. The need for chimpanzees in current and future research has been thoroughly studied and documented in reports that span the last decade.

The essence of the proposed program is to create a colony of behaviorally normal, noncontagious chimpanzees to be used primarily for breeding and to undertake research that will improve reproduction and chimpanzee health and well-being in captivity. While the primary objective of the program is to assure a self-sustaining chimpanzee breeding resource, chimpanzees that are not needed for this purpose would be made available for research purposes. The program would provide financial assistance through cooperative agreements to four or five chimpanzee colonies that now own appropriate breeding

stock. These colonies are planned to contain a total of 250 breeders plus offspring and would initially produce 35 offspring per year at an estimated cost of \$5,000 per year per animal maintained. The program's initial awards are planned for FY 1986.

**Animal Facility Improvement**  
Animal facilities are an integral part of every research institution engaged in biomedical research. Projects to improve research animal facilities (alterations and renovations) have been supported by the Animal Resources Program. From 1971 through 1984, 126 institutions received improvement grants with awards totaling approximately \$17.3 million. Recent awards were limited to \$100,000 for alterations and renovations. A new program initiated in 1985 raised the limit to \$500,000 for alterations and renovations with a 50:50 matching requirement. However, this program did not include authority for new construction and thus did not address the issue of technological obsolescence which has occurred in many

aging and deteriorating facilities. Without new construction capability, many institutions have been unable to institute advanced environmental support systems for animal care and utilization. These needs are reported to be acute in small and minority institutions.

#### *Primate Center Facilities Improvement*

An extensive assessment of Primate Research Center needs was undertaken in 1983 as a result of increasing recognition that facilities and equipment were seriously deteriorating and becoming out of date. Unforeseen expenses have been added this year with legislation that requires new and larger caging to house one of the most common classes of macaque monkeys.

A 5-year program was begun in 1984 to address these needs with funds that were specially designated for this purpose. Through FY 1986, such expenditures will total \$4.5 million with an additional \$1 to 2 million having been contributed from center host institutions. It is anticipated that the current modernization program will be extended beyond the targeted completion date of 1989.

### **Biomedical Research Support Program**

The DRR Biomedical Research Support (BRS) Program is designed to strengthen institutional research in the health sciences. It pursues this goal through three grant programs: the Biomedical Research Support Grant Program, the Shared Instrumentation Grant Program, and the Minority High School Student Research Apprentice Program.

### **The Biomedical Research Support Grant Program**

#### **Purpose**

The general objective of the Biomedical Research Support Grant Program is to strengthen, balance, and stabilize Public Health Service supported biomedical and behavioral research programs. Awards are made to institutions actively engaged in health-related research to provide flexible funds

for research needs not met by other types of PHS grants. Each institution determines how the funds will be used to improve its programs. The flexible funds complement and supplement PHS research grants by providing for short-term, low-cost, interim and shared research resource needs. The BRSG Program thus enables institutions to respond quickly and effectively to meet emerging opportunities and unpredictable requirements that develop during the course of active research programs. BRSG funds may be used to support (1) pilot studies to test the validity of new, innovative ideas or techniques; (2) new investigators, including women and minorities, in establishing research laboratories; (3) centrally shared equipment and upgrading of facilities to meet standards for animal care; (4) interim or emergency funding to save research projects from being interrupted before completion; and (5) unexpected requirements or opportunities that arise during the course of regular research projects.

#### **Program Outcomes**

The BRSG Program supported over 9,000 pilot and regular research projects at 557 institutions in 1985. BRSG-funded pilot studies contributed to the identification of a unique population of cells in the cerebral cortex that appear to trigger epileptic seizures; the development of a data processing system that quadruples the amount of information obtainable with diagnostic ultrasound and promises to enhance the diagnosis of cardiac disorders; and the testing of a new potential cancer drug, dihematoporphyrin, which has an unexplainable toxic effect on cancer cells. The BRSG award also enables recipient institutions to purchase small equipment items and provide support for shared institutional equipment resources. Over the years between 13 and 15 percent of the Program's funds have been used for these purposes.

#### **Policy Issue**

In the FY 1987 President's budget request the Biomedical Research Support formula grant activity will be eliminated. This reduction has been proposed by the Administration to permit NIH to continue to support 18,000 investigator-initiated research project grants, at a time when reductions are required in order to meet the goals of the Balanced Budget and Emergency Deficit Control Act of 1985. NIH will need to assist these research-intensive institutions, which received the awards in previous years, in identifying alternate sources of funding for their research support activities.

### **The Minority High School Student Research Apprentice Program**

#### **Purpose**

The Division's Minority High School Student Research Apprentice (MHSSRA) Program works to attract minority high school students to careers in biomedical research or the health professions. The Program offers minority teenagers opportunity for "hands on" experience in biomedical research. When it began in 1980 the program funded research apprenticeships for 200; by 1985 the number of apprenticeships had increased to 1,008. Assigned to biomedical investigators who are committed to broadening students' scientific understanding and to teaching needed technical skills, the apprentices generally carry out research procedures, collect and analyze data, and report their findings in papers and at seminars. Many apprentices develop close working relationships with graduate and undergraduate students. This experience, which lasts 8 weeks or longer, is intended to cultivate an interest in the biomedical sciences that will motivate the students to pursue careers in health research or a health profession.

#### **Program Outcomes**

An assessment of the FY 1984 program data shows that the program is reaching a number of different minority groups; 56 percent of the student participants were Black, 18

percent Hispanic, 21 percent Asian, and 5 percent American Indian. Female students outnumbered male participants, 59 percent to 41 percent. High school levels represented include sophomores (11 percent), juniors (42 percent), and seniors (46 percent). Almost all the students planned to attend college (98 percent) and a majority of those (68 percent) planned a college major in biological and health sciences. More than half of the students reported that the MHSSRA Program had motivated them to pursue a research career.

## The Shared Instrumentation Grant Program

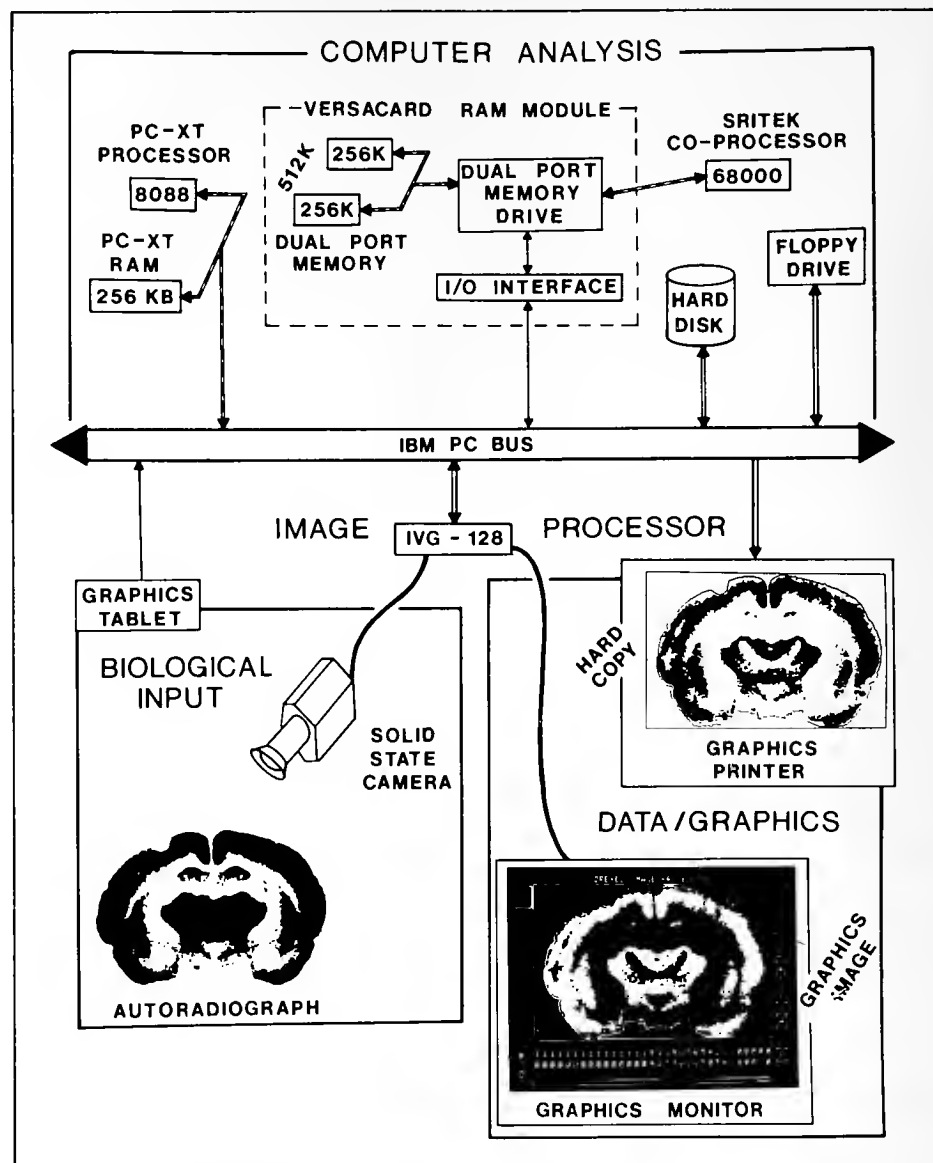
### Purpose

Sophisticated, complex instrumentation plays a crucial role in opening new questions to investigation and extending the boundaries of our scientific frontiers. In 1982, DRR established a special program targeted to large-scale, multi-user instrumentation and designed to encourage sharing among individual investigators, research groups, departments, and institutions. Through the Biomedical Research Support Shared Instrumentation Grant Program, DRR provides support for the acquisition of sophisticated, state-of-the-art instrumentation in the \$100,000 to \$300,000 cost range for groups of PHS-funded investigators on a shared-use basis. Since 1982, the SIG program has received over 1000 applications requesting over \$200 million in instrumentation. Over 500 awards totaling \$99 million have been made to medical schools, graduate schools, research organizations and hospitals to meet research instrumentation needs.

### Program Outcomes

Some accomplishments that have been made as a result of SIG instrumentation awards include:

- Use of a gas phase protein sequencer that allowed the amino acid sequencing of two tumor antigens. In addition, amino acid sequence information was obtained from the antigenic site of the rabies



*Autoradiographs are digitized with a solid state camera, processed by a personal computer, and provided as an enhanced image on the graphics monitor or in hard copy from the graphics printer.*

virus glycoprotein. The protein sequencer has allowed investigators to determine the primary sequences of a range of clinically important antigens.

- Another instrumentation unit is an autoradiographic system that scans slides, autoradiograms, and electrophoretic gels, among other materials, to visually detect data that may indicate the efficiency of blood flow, glucose use, or drug receptor interaction. A digitizing head shines light through or onto the material and collects more than 4 million data points, which are

stored on a computer. An image processor translates and displays this information on a color monitor. Scientists use the instrument to study the brain, the heart, and muscles, as well as subtle changes in cell cultures; in fact, the entire human body can be studied. Researchers in rehabilitation medicine use the instrument to scan photographs of patients to determine how well they are recovering from stroke or arthritis, for example. The image analyzer allows the physician to precisely determine healing progress over a period of time.

## Policy Issues

Suggestions have come from a number of sources, such as studies and reports on instrumentation, the grantee community, and NIH advisors, that the SIG Program consider two policy changes. First, to provide some support for maintenance of the shared instruments for a few years after the purchase. Second, to "lower the floor" to allow the purchase of medium-priced instruments in the range of \$50,000 to \$100,000, in addition to higher-cost instrumentation purchase currently allowed by the program. These and other program policy issues will be examined in an evaluation of the SIG Program and a similar program administered by the National Institute of General Medical Sciences. The evaluation, which will be carried out in FY 1987, will assess whether the programs are meeting their stated objectives, as well as the rationale for their methods of operation. The outcome of this study will be used by DRR staff in reviewing program priorities and in planning future program directions.

## Minority Biomedical Research Support Program

### Purpose

The Minority Biomedical Research Support Program was established in 1972 to increase the numbers of minority biomedical researchers. Institutional grants support the participation of undergraduates, graduates, and faculty in biomedical research. The program serves colleges (2-year and 4-year), universities, and health professional schools in which 50 percent or more of the students are classified as minorities (Black, Hispanic, American Indian, Pacific Islander-Asian). Other institutions with substantial, but less than 50 percent, minority enrollments that have a history of and/or demonstrated special commitment to minority students and faculty are also eligible to participate in the Program.



*Students supported by the Minority Biomedical Research Support Program discuss their research on new anti-inflammatory steroids with their faculty advisor. The MBRS Program serves colleges, universities, and health professional schools in which 50 percent or more of the students are classified as minorities.*

At developing institutions and those where the primary mission is teaching, faculty participants are supported for release time that provides opportunity to engage in research in which they involve their students. The Program provides these institutions funds for equipment, supplies, and renovation of facilities to accommodate research. Faculty with a record of research support at eligible majority institutions having substantial minority enrollments can also participate in MBRS support targeted for salaries for student research assistants.

Four grant instruments carry out MBRS objectives: (1) the traditional MBRS Program Project grant; (2) the Undergraduate College Research Participation grant; (3) the Thematic grant award; and (4) supplemental awards for Shared Instrumentation.

The Program supports research in all of the disciplines and categorical areas of interest to NIH and other PHS research entities: basic research, clinical research, and behavioral studies.

In 1972, the Program made its first awards, totaling \$2 million to 38 institutions. By 1985, the Program expanded to provide support for 95 awards in the amount of \$35.5 million. This includes almost \$11 million in cofunding provided by 10 NIH Institutes, the National Institute of Mental Health, and the National Institute of Alcohol Abuse and Alcoholism. These cofunding agreements were established in 1975 to involve program staff from other Institutes with researchers from minority institutions and thus create a broader base of interaction between NIH staff and the minority community. There have been many spinoffs from this activity. There is enhanced interest and knowledge, among NIH staff about the underrepresentation of minorities in biomedical research. As a result of this interest and knowledge base, other avenues have opened up for increased minority participation in NIH activities and programs. In addition, students and faculty from minority institutions have been able to pursue more categorical interests in research and research training

because they now have more access to program staff from the various NIH Institutes.

### Progress in Meeting Program Goals

The current MBRS portfolio includes 5, 2-year colleges and 46, 22, and 18 institutions that offer as their highest degree baccalaureate, masters, and doctorate degrees, respectively. The MBRS Program supports five grants that serve primarily American Indians, 55 that serve primarily Blacks, eight that serve primarily Puerto Ricans, 15 that serve other Hispanics, and two that serve Hawaiians. The remainder serve a mixed population of minorities in large metropolitan areas and the Southwest.

One measure of success is the number of students who have continued their education beyond the baccalaureate degree. Approximately 7,500 minority students have participated in the MBRS Program since 1972. Of the nearly 5,000 students receiving baccalaureate degrees, about 80 percent have been accepted to graduate, medical, dental, and other health professional schools. The most recent data (1984) about career choices of MBRS graduates shows that of 409 who received B.S. degrees, 86 were accepted to medical schools, 24 to dental schools, 120 to graduate schools, and 93 to other health science schools.

At the University of California, Santa Cruz, the MBRS Program has been successful in motivating an unusually high percentage of its students to enroll in graduate, medical, and dental schools. In 1984, 15 MBRS students received the B.S. degree, with five going to graduate school, seven to medical school, and three to dental school. It was noteworthy that two of those entering medical school were accepted into an M.D./Ph.D. program at Michigan State to prepare for research careers in clinical areas.

The National Academy of Sciences (NAS) Doctoral Record File has identified a total of 199 former MBRS students as having received Ph.D.'s from all Ph.D.-granting institutions reporting to NAS. Of

these, 113 were awarded by MBRS-supported institutions. In a preliminary report, the American Dental Association has identified 94 former MBRS students who have been awarded the D.D.S., and about 53 who are currently enrolled in dental schools. Similarly, the American Association of Medical Colleges' preliminary report lists 617 former MBRS students who have received the M.D. and 580 who are currently enrolled in medical schools.

A second measure of program success is transition to traditional NIH research grant support. At Meharry Medical College, one scientist who has been supported by the MBRS Program for 2 1/2 years to carry out her research on Hydrocortisone Induction of Amino Acid Uptake in Keloid and Normal Fibroblasts has now been awarded an individual research grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases for her project. Over the past 3 years, the MBRS program at this school has had at least one investigator per year move from MBRS support to regular NIH research grants (RO1) support. Last year the institution awarded Ph.D.'s to five MBRS students and in 1986 awards to another four MBRS-supported Ph.D.'s are expected. This is perhaps the best example of the impact of the MBRS Program on one minority institution.

### Research Highlights

#### *Steroids and Breast Cancer*

Primary tumors of about 60 percent of breast cancer patients contain measurable amounts of estrogen receptor protein (ERP). So-called ERP-positive patients are much more likely to benefit from hormonal therapy than are their ERP-negative counterparts. This mode of treatment results in tumor regression in 50 to 60 percent of ERP-positive patients. In contrast, only about 5 percent of ERP-negative patients respond to hormonal therapy. Progesterone receptor protein (PRP) also correlates with Patients responses to hormonal therapy. Patients whose tumors contain measurable levels of both ERP and

PRP tend to benefit most from hormonal treatment. The strong correlation between patient response and levels of ERP and PRP in breast tumor fluid created an obvious need for reliable, highly sensitive indicators that allowed easy detection of the receptors in biological assays.

Researchers have synthesized three iodinated steroids that readily bind to the progesterone receptor in breast cancer cells. Studies show that the compounds can greatly improve the sensitivity of methods now used to determine receptor levels, a reliable indicator of how breast cancer patients will respond to hormonal therapy involving such drugs as tamoxifen.

#### *Immunological Techniques for Early Diagnosis of Schistosomiasis*

An MBRS researcher, who has made numerous contributions to research on different aspects of immune responses to parasites throughout a long and distinguished career, has reported progress in both diagnosis and development of a vaccine for schistosomiasis. He has produced highly refined, species-specific antigens to the causal parasite. Using monoclonal antibody techniques, these antigens will allow immunodiagnosis at earlier stages of the disease. The newly isolated antigens may also be used in the development of a vaccine.

He is also conducting related work on the liver fluke that causes cirrhosis in sheep, cattle, and humans. He has developed a new serological method of diagnosis of this infection in asymptomatic humans.

### Future Opportunities and Priorities

#### *Faculty Research Career Enrichment Awards*

Relatively few faculty at MBRS-eligible undergraduate institutions have been successful in competing for nontargeted research support. In addition, a large number of faculty at these colleges have had a low success ratio when competing for



support in the MBRS renewal application process. The initial research efforts of these faculty must compete with conflicting demands of heavy teaching and administrative workloads. These interfere with their ability to spend time in keeping current in their fields and developing or learning needed new research techniques.

MBRS program staff and advisors propose to institute Research Career Enrichment Awards to update and expand faculty research capabilities at these smaller institutions. These grants would provide off-campus research experiences at leading research laboratories for periods of up to 1 year. The award would allow faculty to initiate research and develop competitive research projects for future MBRS or other research support with consequent opportunities for continuing collaboration with scientists at host laboratories. These awards would be available only to faculty who are holders of the terminal degree at undergraduate institutions with 50 percent or more minority student enrollment or with a substantial minority student enrollment, and a history of commitment to training minorities. Health professional schools and other institutions that offer the doctorate degree would not be eligible.

#### *Animal Resources Improvement Grants for Minority Biomedical Research Support Institutions*

Many minority institutions will be adversely affected by the requirements of the newly revised Policy on Humane Care and Use of Animals by Awardee Institutions because of the lack of animal facilities that can meet the new requirements and resources to address the problem. Research and research training using live animals at these institutions may cease unless their needs can be met.

Thus the MBRS Program plans to award supplements to ongoing MBRS grantees for improving animal facilities, training personnel, and purchasing caging and associated equipment. Support would be provided for costs such as: alteration and renovation of

animal facilities, purchase of cages and cage-washing equipment, training of personnel in the care and use of animals for research, and consultation needed for improvement and management of facilities. It is estimated that between 18 and 30 institutions may have severe needs for such supplements.

### **Research Centers in Minority Institutions Program**

#### **Purpose**

The Research Centers in Minority Institutions Program was congressionally mandated in FY 1985. Funded through an appropriation to the Office of the Director, NIH, it is administered by the Division of Research Resources. The purpose of the Program is expansion of research in the health sciences by assisting, through grant support, predominantly minority institutions that offer the doctorate in either the health professions or health related sciences. The RCMI Program is intended to strengthen the research environment, both human and physical resources, at these institutions and thus enhance capacity for the conduct of biomedical and behavioral research.

#### **Progress Toward Meeting Program Goals**

RCMI-participating institutions are likely to expand their contributions to biomedical research as well as to biomedicine. For example, at Meharry Medical College in Nashville, Tennessee, part of the RCMI grant is providing support for the development of a research capacity in neuroscience which can ultimately be expected to expand knowledge relevant to nervous system function and dysfunction. This work will contribute to a better understanding of the etiology of essential hypertension and stroke, including motor defects resulting from stroke.

At another RCMI-supported institution, Howard University in Washington, D.C., an immunogenetics laboratory for the investigation of kidney diseases,

cancer, diabetes, hypertension, sickle cell disease, and infectious diseases is under development.

At Hunter College, a component of the City University of New York, the RCMI award will support the development of a major molecular biology research center to study gene structure and function. A major NMR laboratory for *in vivo* metabolic studies will be established, along with expansion of present x-ray crystallographic research.

#### **Future Opportunities and Priorities**

The current plans include expansion of existing support to current grantees and support for additional eligible institutions.

# **The Biennial Report of the Director, John E. Fogarty International Center for Advanced Study in the Health Sciences**

## **History**

The following events represent milestones in the development of the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC).

- January 1967—Representative Melvin Laird proposed to Congress the establishment of an international research and study center at the NIH as a memorial to the late Representative John E. Fogarty of Rhode Island. Subsequently, President Johnson announced that he was seeking funds for the establishment of the John E. Fogarty International Center for Advanced Study in the Health Sciences.

- November 1967—P.L. 90-132 included funds for initial planning.

- February 1968—The Department of Health, Education, and Welfare granted approval for establishment of the FIC.

- July 1968—The NIH Office of International Research was abolished, and several of its functions were transferred to the FIC.

- 1971—The FIC annual appropriation provided core funding for the Gorgas Memorial Institute and Gorgas Memorial Laboratory, formerly funded through NIAID/NIH and the Department of State.

- March 1981—The Director of the FIC was granted a dual appointment as NIH Associate Director for International Research. All subsequent FIC Directors have served both functions.

- 1984—Dr. Craig K. Wallace was appointed Director of the FIC.

- July 1984—The FIC Advisory Board was authorized by Secretary of the U.S. Department of Health and Human Services.

- November 1985—The FIC was established in the Public Health Service Act as amended by P.L. 99-158, Sec. 482.

## **Introduction**

The mission of the FIC is to facilitate the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of health science internationally and to coordinate the activities of the National Institutes of Health in this area. In addition, the FIC provides postdoctoral fellowships for research training in the United States and abroad and promotes exchanges of senior scientists between the United States and other countries.

The FIC operates through four programs: Advanced Studies, International Research and Awards, International Coordination and Liaison, and Foreign Scientists Assistance. The FIC Director is also the NIH Associate Director for International Research, in which capacity he advises the NIH Director on the development of international policies and procedures related to biomedical science. The FIC also provides the U.S. Government core support for the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc. (GMI), in Washington, D.C., and the Gorgas Memorial Laboratory (GML) in Panama.

International relationships of the NIH cover the broad range of activities from participation in collaborative basic research, applied research, and clinical investigation, to intervention studies and professional and public education, including the transfer of research knowledge to clinicians. Mutual benefits accrue not only in advancing scientific knowledge but also in improving diagnostic capabilities and health care.

## **Advanced Studies**

The FIC Advanced Studies Programs provide opportunities to address broad concerns in biomedicine by involving leading research scientists from around the world. International forums are provided for the exchange of information and for the review and evaluation of major

areas of biomedical research, particularly those related to health problems of interest to the NIH. Advanced international studies in the health sciences are conducted by the International Studies and Scholars-in-Residence programs.

## **International Studies**

International studies focus on health problems of global significance and may influence the formulation of treatment and prevention strategies. A primary goal is to identify and address issues concerning international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to benefit international health. The International Studies Program identifies barriers to the international transfer of research findings and develops methods to overcome these barriers. The following recent accomplishments and plans exemplify international biomedical science cooperation.

In 1980, the International Studies Program began an effort to focus world attention on the potential for eradicating selected infectious diseases; a number of infectious disease candidates were evaluated for improved control and potential eradication. Four international reviews have been held since then on measles, paralytic poliomyelitis, congenital rubella infection, and yaws and other endemic treponematoses (parasites). A systematic reexamination of both research needs and progress toward eradication of the targeted diseases began in FY 1985. A workshop to review the scientific aspects of antibiotic usage and resistance worldwide was held in 1986.

The FIC and the World Health Organization are studying jointly the potential for integrated infectious disease control efforts. They have held an Africa-wide regional meeting on yaws and other endemic treponematoses as a followup to the regional conference held in July 1985 in Cipanas, Indonesia.

In 1987, the FIC will organize and sponsor, on behalf of the NIH and PHS, an international meeting on

acquired immune deficiency syndrome (AIDS). A study on research toward rabies prevention is also scheduled for 1987.

### **Scholars-in-Residence**

The Scholars-in-Residence Program was established in 1969. Outstanding scientists and scholars are invited to the NIH to collaborate with the scientific community and to contribute to the NIH intellectual environment through research seminars, lectures, and conferences. Scholars pursue individual studies of subjects of mutual interest to them and the NIH. Appointments are for up to 12 months and must be completed within 4 years from the date of the invitation. This program offers scholars the unique opportunity to focus on research and writing that they might not otherwise be able to undertake. A total of 131 scientists from 24 countries have participated in the program. Most have come from Western Europe, North America, Japan, or Australia. In FY 1985, 31 scientists, 10 of whom were newcomers, participated in the program.

The collected bibliography of scholars who have participated in the program now consists of more than 500 titles, including over 60 monographs, numerous reviews of major topics in biomedical research, and over 400 original articles in international journals. Scholars have, for example, published papers on the development of vaccines against leprosy; the development of synthetic antigens for preparation of hepatitis vaccines; the relationship between cellular oncogene expression and hematopoietic development; the characterization and synthesis of information-bearing peptides; and the molecular, genetic, and clinical aspects of hemoglobin.

A long-term collaboration between two scholars from different countries led to a joint publication in 1985, with their respective collaborators, which showed that the genetic regulation of lectin (protein) biosynthesis plays an important role in control of cell-to-cell adhesion

during embryogenesis. An important aspect of the continuing collaboration has been the ability of the two laboratories to exchange key scientists.

Other studies have addressed a variety of topics including the regulation of gene expression during embryogenesis; development of more sensitive methods for determining the structure of complex polysaccharides; chemotactic substances and the migration of metastasizing cancer cells; role of receptor molecules in growth of tumor cells; characterization of defensive chemicals in insects; analysis of proteins related to ossification of developing bone tissue; development of special absorbents for purification of complex subcellular organelles; and the role of disturbances of axonal transport processes in nerve cells related to specific neuroaxonal dystrophies in humans.

### **International Research and Awards**

The FIC administers and provides full or partial support for several types of international fellowship programs. These programs facilitate the exchange of research experiences and information by enabling foreign scientists to pursue their research interests in U.S. laboratories and by providing opportunities for U.S. researchers to work in foreign laboratories.

#### **International Research Fellowships**

The International Research Fellowship (IRF) Program enables postdoctoral biomedical and behavioral scientists in the formative stages of their research careers to extend their research experience through work in a U.S. laboratory. These fellowships forge relationships between distinguished U.S. scientists and qualified scientists in other countries that allow them to conduct research on health-related problems of mutual interest. Their research areas cover the breadth of NIH interests, but focus primarily on cancer and cardiovascular and infectious diseases.

During FY 1985, there were 54 participating countries or geogra-

phic areas, each eligible to nominate up to six candidates per year for the IRF Program. Thirty-six committees recommended applicants, 155 applications were peer reviewed, and 100 applications (64 percent) were funded. The recipients, from 31 countries, were funded for work in 25 states. Examples of collaborative research undertaken by IRF awardees in FY 1985 are the following:

- The IRF program enabled postdoctoral biomedical and behavioral scientists to carry out research on the induction and action of interferon, a protein used in the prophylaxis and treatment of a number of human viral infections. The scientists were able to demonstrate that in a herpes virus-transferred lymphoblastoid cell line, the increased antiviral activity registered upon heat-induction was due to de novo synthesis of a new interferon-like lymphokine. This heat-induced interferon may be a different type because its physicochemical and biological properties are somewhat different from other known isolates of human interferons.

- A Fellow worked with U.S. researchers on the rejection process in lung allografts of rats. Specifically, these scientists the etiology of obliterative bronchiolitis in transplanted lungs, determined the immunosuppressive potency of a new cyclosporine derivative, and developed a new transplantation technique for investigating combined heart-lung grafts. Results of their work will help to enhance the effectiveness of heart-lung transplantation procedures.

#### **Senior International Fellowships**

The Senior International Fellowship (SIF) Program provides opportunities for established U.S. biomedical or behavioral researchers to conduct collaborative research in foreign institutions. SIF awardees enhance the exchange of ideas and information about the latest advances in specific areas of medicine. This collaboration leads to improvement in the research, education, and clinical

potential of the U.S. institutions, which profit from the scientists' experiences abroad. During FY 1985, U.S. institutions nominated 90 scientists for the SIF Program. Of those nominated, one-half were funded.

Examples of collaborative research projects undertaken by SIF awardees in FY 1985 are the following:

- A Senior International Fellow was able to apply current techniques in immunology to study the immune response during toxoplasmosis infection with a specific strain of *Toxoplasma gondii* in animal models. This Fellow, interested in toxoplasmosis since 1965, had the opportunity to work in an immunology laboratory of international repute, thus enhancing his research career, previously more clinical-oriented than basic.

- Another Fellow collaborated with researchers on an important problem in cellular neurobiology. These researchers were able to create an immortal rat cell line of brain origin by transforming cultures of optic nerve cells with a virus. The technique that they developed will have wide applicability for immortalization and transformation of a variety of cell types from the mammalian central nervous system. It will also accelerate study in neurobiology at the cellular and molecular level.

#### **Foreign Fellowships for U.S. Scientists**

Six postdoctoral research programs for U.S. scientists to study abroad are administered by the FIC and supported by the respective governments of Finland, France, Ireland, Norway, Sweden, and Switzerland. The FIC also announces the availability of fellowships supported by the Alexander von Humboldt Foundation in the Federal Republic of Germany and by the National Science Council in Taipei, Taiwan.

#### **Individual Health Scientist Exchange Programs**

Under individual cooperative agreements, the FIC administers health scientist exchange programs with seven countries: Bulgaria,

France (the National Center for Scientific Research [CNRS]), Hungary, Poland, Romania, Soviet Union, and Yugoslavia. These exchanges are on a shared-cost basis, with the host country paying in-country costs and the sending country supporting travel.

#### **Research Needs and Future Opportunities**

Research fellowships or other extramural opportunities that should be pursued in the future include special initiatives in the following areas:

- Biotechnology—to establish and maintain collaborative relationships with scientists in other countries in the forefront of scientific areas.

- AIDS—to enable researchers to obtain additional knowledge about the disease and to develop a cadre of young researchers, or to focus on developing countries.

Special program opportunities include the following:

- A research fellowship program for junior U.S. postdoctoral scientists to take advantage of research advances in other countries.

- A senior foreign scientist research fellowship award to stimulate the transfer of scientific knowledge to the United States.

#### **Special Foreign Currency Program**

The Special Foreign Currency Program (SFCP) supports biomedical research in the health sciences in selected countries. The SFCP is collaborative in character, comprises projects covering a wide spectrum of biomedical and health sciences, and draws upon resources unique to the host country.

In FY 1985, 19 NIH projects in the amount equivalent to \$314,000 were approved and funded in Yugoslavia. One newly funded project will focus on gastrointestinal cancer in high- and low-risk areas of Yugoslavia. This is a 3-year case-control study involving three cancer sites—the stomach, colon, and rectum. Information gained from this study will be useful to the U.S. population as well, because 5 percent of all deaths between 1971 and 1981

were due to malignant neoplasms of the digestive organs and peritoneum.

In FY 1985, 28 NIH projects were approved and funded in India. One 3-year study there involves viral hepatitis and has several objectives: (1) to study the population-at-risk in relation to several different strains of hepatitis virus, (2) to develop the technology to diagnose and study the epidemiology of viral hepatitis, and (3) to develop the expertise of central testing facility staff with the capability to transfer this technology to other centers in India. The project is well under way, and results will be useful to developed and developing countries.

#### **International Coordination and Liaison**

The United States makes significant contributions to the resolution of a broad spectrum of international health problems through its domestic research, its cooperative health relationships with other countries, and its participation in the programs and activities of international organizations, notably the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

The International Coordination and Liaison (ICL) Program of the FIC facilitates and promotes NIH relationships with other countries through arrangements for interaction between scientists, exchange of scientific information, and communications between the NIH and other international organizations or agencies. Program management staff provide policy guidance, coordination, and general oversight for NIH participation in bilateral and other cooperative agreements between the United States and other countries, between DHHS and counterpart ministries in other countries, and between the NIH and similar institutions abroad.

#### **Bilateral Activities**

In FY 1985, the NIH participated in 53 bilateral agreements with 31 countries. The FIC is the lead PHS agency for bilateral programs with Belgium, France, Federal Republic

of Germany, Hungary, Japan, Poland, Romania, Venezuela, and Yugoslavia.

Significant events that occurred during FY 1985 include the following:

- The French National Institute of Health and Medical Research (INSERM) and the NIH signed a Memorandum of Understanding in October 1984 to facilitate cooperation in the fields of cancer research; cardiovascular disease research; pulmonary disease research; immunology, tropical medicine, and infectious diseases; neurosciences; technological evaluation; and instrumentation and biomedical engineering.

- In March 1985, the U.S.-Spain Joint Science and Technology Committee approved funding for eight cooperative research projects endorsed by the NIH. Three of the awards were made to NIH investigators and five to extramural scientists.

- The Indo-U.S. Science Technology Subcommission met in New Delhi in April 1985. The subcommission's Health, Medical, and Life Sciences Working Group noted the significant progress that had been made since the last meeting in 1981, notably that 23 projects were implemented under the Indo-U.S. Science and Technology Initiative. The working group strongly endorsed cooperation on immunization and vaccine development, and subsequently, a Vaccine Action Program was announced during the Summit Meeting between President Reagan and Prime Minister Rajiv Gandhi in June 1985. Collaboration is expected in several areas, including hepatitis, pneumococcal pneumonia and cholera, and the development of vaccines using DNA technology.

- In April 1985, the Fourth Meeting of the U.S.-People's Republic of China Joint Commission on Science and Technology was held in Washington, D.C. The commission reviewed progress under the 22 cooperative protocols and noted its satisfaction with accomplishments in the health area. These included collaborative epidemiological studies of cardiovascular disease and trials of

hepatitis vaccine; new projects implemented in the public health area; and establishment of a Memorandum of Understanding between the NIH and the Chinese Academy of Sciences for cooperation in basic biomedical fields.

- In May 1985, the FIC sponsored the visit of a delegation of U.S. biomedical research scientists to Romania to participate in the Fourth U.S.-Romania Workshop on Biomedical Research. The workshop, which was held under the auspices of the U.S.-Romania Individual Health Scientist Exchange Program, was devoted to the topic of Cellular and Molecular Events in Atherogenesis. The workshop was organized jointly by the National Heart, Lung, and Blood Institute and the Romanian Institute of Cellular Biology and Pathology.

- The U.S.-Korea Subgroup on Science and Technology met in Washington, D.C., in June 1985. The subgroup heard status reports on cooperation in a number of fields, including health, and noted that the two proposals in toxicology and genetic engineering showed promise for collaboration. The Korean representatives noted that a new center for genetic engineering research had been established in 1985 at the Korea Advanced Institute for Science and Technology (KAIST), and they outlined their plans for future cooperation.

- Following the establishment in 1983 of a U.S.-Mexico Joint Working Group on Health under the U.S.-Mexico Mixed Commission on Science and Technology, the NIH initiated research collaboration with the Instituto del Seguro Social and with the Centro de Desarrollos y Aplicaciones Technologicas in the Secretaria de Salud.

A number of significant research advances were made by components of the NIH in FY 1985 under bilateral agreements coordinated by the Fogarty International Center. Some examples of these advances are the following:

- The results of an 8-year study, supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)

and involving 71 medical centers in North America, Europe, and Asia, showed that the extracranial/intracranial (EC/IC) bypass operation, a neurosurgical procedure that directs blood past occluded brain arteries, should be abandoned in favor of safer, equally effective medical alternatives. This study, which demonstrated to the surgical community that controlled clinical trials of a surgical procedure are ethical and feasible, has set an international standard for the evaluation of surgical procedures.

- Under the Medical Science and Public Health Cooperative Agreement with the Soviet Union, cooperative research was conducted on the effects of microwave radiation and low-frequency electromagnetic fields on the nervous, cardiovascular, and reproductive systems. In addition, a collaborative research protocol was developed to identify (a) more reproducible biological endpoints for assessing the effects of nonionizing radiation and (b) more sensitive indicators of biological alterations. These joint experiments will serve to resolve the longstanding discrepancy between U.S. and Soviet safety standards for electromagnetic radiation.

### **Multilateral Organizations**

The FIC represents the NIH in contacts with multilateral bodies such as WHO, PAHO, the European Medical Research Councils, the European Science Foundation, the Organization for Economic Cooperation and Development, and the Commission of European Communities.

The FIC, as a WHO Collaborating Center for Research and Training in Biomedicine, has promoted mutually beneficial interactions among the NIH, WHO, and PAHO. In FY 1985, the FIC, WHO, and PAHO developed two cooperative projects involving several U.S. Public Health Service agencies, the Bureau of Science and Technology for International Development of the National Research Council, the U.S. Agency for International Development, Canada's International Research

Development Centre, and ministries of health in Central and South America and the Caribbean. One project, to assess education and training needs for medical entomologists engaged in the research and control of vector-borne diseases in the Americas, resulted in recommendations for action by the ministries of health of Guatemala, Colombia, Ecuador, and Panama. The second project, to develop strategies for strengthening health research capabilities in six Latin American countries through international collaboration, is under way.

### Gorgas Memorial Laboratory

The FIC serves as the channel for U.S. Government core support to the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc. (GMI), in Washington, D.C., and its operating arm, the Gorgas Memorial Laboratory (GML) in Panama. The FIC maintains general program oversight for the funding of the GML, which represents approximately two-thirds of the total GML budget.

The GML conducts a diversified program of research on tropical diseases, especially those endemic to Panama and neighboring countries. Particular emphasis is placed on virology, parasitology, and the effects of environmental change on disease vectors and transmission. Recently the GML has undertaken studies of other public health problems, e.g., cervical cancer and HTL virus.

The GML also provides special diagnostic and reference services, epidemic investigations, and surveillance of vector-borne diseases; and it conducts formal and informal research training for scientists and technicians from the United States, Panama, and other countries. It has cooperative arrangements with several U.S. universities for graduate and medical students. Formal training courses in tropical medicine are conducted several times a year for U.S. Navy medical officers. The GML also maintains the major biomedical library of the region.

During 1985, the FIC assisted in program planning efforts of the GML through sponsorship of two scientific site visits, one in parasitology and the other in virology and epidemiology. These provided advice on future research directions and technologies. A site visit on clinical research is planned for 1986.

### Foreign Scientists Assistance

The FIC Foreign Scientists Assistance Program provides coordination, guidance, and facilitative services to NIH research Institutes and Divisions in the administrative management of the NIH Visiting and Guest Researcher Programs. This program links NIH activities with those of other components of DHHS, the Immigration and Naturalization Service of the Department of Justice, the Department of State, the United States Information Agency, and foreign embassies and science attaches. The NIH programs offer the opportunity for talented scientists throughout the world to engage in collaborative research with NIH scientists. In FY 1985, scientists from over 60 countries participated in NIH intramural programs.

### Conclusion

The FIC has created and is continuing to develop a network for dynamic ever-expanding worldwide scientific communication and interaction. Over 2,300 foreign scientists from approximately 50 countries have conducted scientific research in U.S. laboratories as a result of the FIC International Research Fellowship Program. Some 130 scholars have come to the NIH for advanced study with NIH intramural scientists. More than 450 U.S. scientists have conducted research in 35 countries. In addition, several important international studies, notably on infectious diseases, have been conducted. Thus the FIC has been able to make many contributions toward international biomedical research collaboration.

## The Biennial Report of the Director, National Library of Medicine

### History

The following events represent milestones in the development of the National Library of Medicine (NLM).

- 1836—The National Library of Medicine was originally established as the Library of the Army Surgeon General's Office.

- 1865-1895—Under the direction of Dr. John Shaw Billings, NLM's mission was expanded and services were made available to physicians generally. The appearance in January 1879 of the first issue of *Index Medicus* and, in 1880, of Volume 1 of the *Index-Catalogue of the Library of the Surgeon General's Office*, are landmark events in NLM's provision of services to health professionals that has continued to the present day.

- January 1922—The Library of the Army Surgeon General's Office was renamed the Army Medical Library.

- April 1952—The Army Medical Library became the Armed Forces Medical Library.

- October 1, 1956—NLM was designated the National Library of Medicine by an act of Congress (P.L. 84-941), and placed within the Public Health Service (PHS).

- January 1964—The Medical Literature Analysis and Retrieval System (MEDLARS) became operational at NLM.

- October 22, 1965—The Medical Library Assistance Act of 1965 (P.L. 89-291) was enacted, providing for an NLM extramural program of grants to expand and improve medical library and health communications resources, technology, and manpower.

- January 1, 1967—A Toxicology Information Program was established at NLM in response to recommendations of the President's Science Advisory Committee.

- July 1, 1967—The National Medical Audiovisual Center (NMAC), became a component of NLM.



systems at NLM with a fully integrated automated system for controlling such functions as acquisitions, cataloging, indexing, circulation, and inventory of the NLM collection.

A Unified Medical Language System (discussed below) will enhance the ability of health professionals and researchers to retrieve medical information without extensive training, as will Grateful Med, the user-friendly system recently developed by NLM for searching MEDLINE on a microcomputer. This software package is available for general distribution through the National Technical Information Service. It translates the user's search request into appropriate system commands, logs on and off the NLM system automatically, downloads citations retrieved to the microcomputer, and suggests terms from NLM's controlled vocabulary that may be appropriate to the user's search. NLM regards the package as part of its continuing effort to improve information services for the U.S. biomedical community.

### Medical Informatics

Since 1973, NLM has been the sole NIH source of grants for training associated with computer applications in medicine. In 1979, NLM also initiated a complementary effort for support of research projects, program projects, and research career development in this field. This comprehensive training and research assistance accounted for approximately 45 percent of available extramural program funds in FY 1984 and 1985. Projected 1986 resources will insure limited continuation of the initiatives and the honoring of commitments in this developing scientific discipline.

American medicine has been a leader in using and developing new technologies to advance the understanding of life processes. Nowhere is this more apparent than in the utilization of the computer in the health sciences where the progress has been truly remarkable and is widely publicized. As experience with computer technology in

research and patient care has grown, attention has shifted from using the computer as a tool to exploiting it as an adjunct to human cognition. Although research into the organization, synthesis, and utilization of information by computers is just beginning, it is clear that the potential uses of artificial intelligence systems in medicine are great indeed.

As a developing field of applied science, medical informatics needs stability of funding and the concentration of human intellectual resources to achieve critical mass. The challenge of medical informatics is to analyze, synthesize, organize, and represent in effective format the available knowledge in specialized fields of medicine. Incorporating both research and training features, Centers of Excellence will provide for increased visibility and stability for the field of medical informatics. In each Center, NLM will support training of highly skilled career investigators, provide adequate core research funding, and support career development programs for experienced researchers. In this way, at the Nation's best academic institutions, the NLM will develop a highly trained cadre of researchers, conduct advanced research activities, and provide long-term career support and job opportunities to keep these talented individuals in this highly important field.

### Expert Systems

One of the primary functions of the NLM is the transfer of biomedical knowledge to researchers and health care practitioners. The knowledge may be embodied in a book, a journal article, an image or a series of images, or more recently, in a computer program. When the problem to be addressed is one of inadequate access to the expertise of human subject matter specialists, the dissemination of the human expert's knowledge may be accomplished through access to consultation via a computer-based expert system. NLM has the opportunity to build on existing strengths and experience both to explore means of representing medical knowledge in

expert systems and to demonstrate the feasibility of delivering this knowledge to those for whom it is not otherwise readily available.

Computer scientists have recently developed tools for building programs that provide a good functional equivalent to human cognition and decision-making when the reasoning domain is relatively narrow. Examples are found in robotics, space exploration, and petroleum geology. More recently, scientists have discovered forms of knowledge representation suitable for reasoning in medicine. The result is an emerging capability to build systems (for the moment at the research level) which can give reliable and practical expert consultation concerning patient diagnosis and management, for use by nonexpert physicians.

The creation of individual expert consultation systems has been supported by research project grants from NLM, and by substantial support from the Division of Research Resources in providing specialized hardware/software resource sites for artificial intelligence research and development. The field now needs a means for evaluating the generality of these systems beyond their home institutions and for validating their utility and medical importance in the national framework.

NLM has the opportunity to work with several specific systems in seeking to develop the technique, structures, and arrangements which may represent a general solution to the validity and utility problems. This does not necessarily involve the conduct of clinical trials *per se*. Furthermore, the cooperation of relevant categorical Institutes will be sought in evaluating particular expert systems.

NLM now has two in-house functioning medical expert systems that have been in development for several years. The AI/RHEUM (Artificial Intelligence/Rheumatology) system for consultation in rheumatology has a diagnostic component ready for national field trials and multi-site validation, and also a patient management and therapy

component ready for extension from rheumatoid arthritis to additional diseases. AI/COAG (Artificial Intelligence/ Coagulation), a second expert system at NLM, deals with problems of human hemostasis. It will also warrant field testing in the near future.

### **Integrated Academic Information Management Systems (IAIMS)**

The IAIMS concept is the integration of computer and communications networks to transform a health institution's various information bases into a single system. NLM's current activity in this area is support of strategic planning and model testing for the development of integrated information systems in the health sciences.

Two recent studies by the Association of American Medical Colleges have identified the need to assist academic medical centers in the United States in planning and implementing institution-wide integrated information networks. The studies also revealed serious gaps in academic information delivery systems. The highly efficient bibliographic networks developed over the past 17 years are not well integrated with internal medical center information systems. These internal systems, furthermore, are often proliferating in an uncoordinated fashion. The majority of academic health center faculties lack sufficient knowledge to exploit emerging technologies to improve information utilization in education, research, and patient care. Libraries and their staffs, along with faculties, need to update their technological capabilities.

Although health care is extremely information-intensive, until very recently, little attention and fewer resources have been devoted to the systematic capture, storage, management, and delivery of academic medical knowledge in medical centers. Experiments with medical data management systems have exposed the fundamental difficulties and complex nature of information handling. While research proceeds to investigate these areas, the rapid

adoption of state-of-the-art information technologies for handling academic information is exceptionally timely.

Medical education is beginning to shift from a memory-based to a conceptual and problem-solving orientation, supported by a variety of information systems. A recently completed national assessment of the general professional education requirements of the physician has identified the importance of this shifting emphasis. Administrators are becoming aware that managing information, like managing financial, human, and physical resources, is a fundamental responsibility of medical centers.

### **The Technological Innovations in Medical Education (TIME) Project**

As part of its mission to assist health professional education through information technology, the Lister Hill Center for Biomedical Communications TIME Project is exploring the use of interactive videodisc, microprocessor, and voice recognition technology to create patient simulations for medical students in all phases of their training. These educational simulations embody dramatic, engaging portrayals of the medical and social condition of a patient and allow uncued, verbal intervention by the student while he or she makes independent clinical decisions.

The first of these simulations concerns a 46-year old man (played by a professional actor) who comes to the emergency room complaining of weakness and abdominal pain following an episode of vomiting blood 2 days earlier. The student, using a microphone and a command vocabulary, takes the patient's medical history and decides how to manage him. If the student admits the patient, the scene changes to the hospital where he or she must make the decisions concerning diagnostic procedures and clinical management of the patient. Should a crisis occur during the hospital stay (i.e., hemorrhage, myocardial infarction, delirium tremens, etc.), the student must intervene or observe the consequences of failure to intervene.



*TIME Project*

### **Unified Medical Language System**

For decades the major fundamental impediment to widespread adoption of computer-based information systems in medicine has been the absence of standardization in vocabulary, terminology, definitions, and criteria for recording the results of biomedical research, the events of clinical patient care, and the managerial and business transactions of hospitals. One major exception is the widespread adoption of the NLM MEDLARS system for access to bibliographic citations of the scientific literature, based on the Medical Subject Headings indexing system.

NLM is taking the lead in planning and developing a computer-based system that will provide the foundation for linking computer systems in the medical and scientific literature with clinic and hospital records, instructional media, and administrative files. In FY 1986, NLM received an additional \$1,000,000 for the initial steps of this major program. The program will be guided by an advisory committee whose members include representatives of groups such as the American Medical Association, university investigators in academic departments, health professional associations, the health insurance industry, and relevant Government agencies. Constituent parts of the system will include such items as terminology, a dictionary, a thesaurus, cross-indices between selected codifications, automated classification and indexing assistance tools, computer programs to validate literature and medical

records concerning their employment of the standards, and computer programs that can assist in updating and maintaining the documents and systems that are implied in this system. The parts will take the form of computer programs and printed publications to be used and tested by collaborating publishers, medical schools, information vendors, and agencies. These will be released for public testing at milestone points beginning two years after initiation of full funding.

### **Summary**

NLM's long range plan will guide the Library's programs for the next 20 years. As the NLM looks back at its proud 150-year history, and acknowledges its present role as the world's premier medical library, it must consider also how best to continue this tradition of service and excellence into the 21st century.



*Sesquicentennial Exhibit in NLM Lobby*



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